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PTO/SB/05 (12/97)

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No. T1427

Total Pages 61

First Named Inventor or Application Identifier

JOSE LUIS CASTRO PINEIRO

Express Mail Label No.

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jc594 U.S. PRO
09/392406

09/09/99

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. ☒ Fee Transmittal Form
(Submit an original, and a duplicate for fee processing)
2. ☒ Specification [Total Pages 58] 1
3. ☐ Drawing(s) (35 USC 113) [Total Sheets 0] 1
4. Oath or Declaration [Total Pages 3] 1
 - a. ☒ Newly executed (original or copy)
 - b. ☐ Copy from a prior application (37 CFR 1.63(d))
(for continuation/divisional with Box 14 completed)
[Note Box 5 below]
 - i. ☐ **DELETION OF INVENTOR(S)**
Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33 (b).
5. ☐ Incorporation By Reference (useable if Box 4b is checked). The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
6. Nucleotide and/or Amino Acid Sequence Submission (if applicable, all necessary)
 - a. ☐ Computer Readable Copy
 - b. ☐ Paper Copy (identical to computer copy)
 - c. ☐ Statement verifying identity of above copies

ADDRESS TO: Assistant Commissioner for Patents
Box Patent Application
Washington, DC 20231

ACCOMPANYING APPLICATION PARTS

7. ☐ Assignment papers (cover sheet & document(s))
8. ☐ 37 CFR 3.73(b) Statement (when there is an assignee) ☐ Power of Attorney
9. ☐ Information Disclosure Statement (IDS)/PTO-1449 ☐ Copies of IDS Citations
10. ☒ Preliminary Amendment
11. ☒ Return Receipt Postcard (MPEP 503) (Should be specifically itemized)
12. ☒ Certified Copy of Priority Document(s) (if foreign priority is claimed)
13. ☐ Other:

14. If a CONTINUING APPLICATION, check appropriate box and supply the requisite information:

☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No. ____/____

15. CORRESPONDENCE ADDRESS

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EXPRESS MAIL CERTIFICATE

DATE OF DEPOSIT September 9, 1999

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MAILED BY Gene Samuels DATE Sept. 9, 1999

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Assistant Commissioner for Patents
Washington, D.C. 20231

Deposit Acct. 13-2755
MERCK & CO., INC.
Our Case Docket No. T1427

Sir:

Transmitted herewith for filing under 37 C.F.R. §1.53(b) is the patent application of Inventor(s):
JOSE LUIS CASTRO PINEIRO, GEORGE MCALLISTER, MICHAEL GEOFFREY NEIL RUSSELL

* For: INDOLE AND INDOLINE DERIVATIVES AS 5-HT6 SELECTIVE LIGANDS

For	Number Filed	Number Extra	Rate	Basic Fee \$760
Total Claims	18 - 20 =	0 X	\$18	= 0.00
Independent Claims	2 - 3 =	0 X	\$78	= 0.00
Multiple Dependent Claims*		X	\$260	=
* Add this fee if application contains any multiple dependent claims, regardless of number.		TOTAL FILING FEE →		\$760.00

Please charge my Deposit Account No. 13-2755 in the amount of \$ 760.00 . The Assistant Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Account No. 13-2755.

Duplicate copy of this sheet is enclosed.

☐ Under the provisions of 37 C.F.R. §1.53, this application is being filed without the declaration of each inventor.

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MAILED BY James L. McGinnis

DATE Sept. 9, 1999

Respectfully,

By: James L. McGinnis

Attorney For Applicant(s)

Reg. No. 34,387

MERCK & CO., INC.

Patent Dept., RY60-30

P.O. Box 2000

Rahway, N.J. 07065-0907

(732) 594- 0641

Date: September 9, 1999

IN DUPLICATE

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Jose Luis Castro Pineiro, et al.

Serial No.: To be assigned

Case No.: T1427

Art Unit:

Filed: To be assigned

Examiner:

For: Indole and indoline derivatives as 5-HT6 selective ligands

Assistant Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Dear Sir:

This application claims priority from Great Britain Application No. 9820113.0, filed September 15, 1998, a certified copy of which is enclosed herewith. Prior to examination of the claims, please amend the claims as recited below.

EXPRESS MAIL CERTIFICATE

DATE OF DEPOSIT September 9, 1999

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MAILED BY Deane Samuels

DATE Sept. 9, 1999

IN THE CLAIMS:

In Claim 2, line 2, please correct the spelling of "accorance" so that it reads -- accordance --.

In Claim 3, line 1, please delete the phrase "or Claim 2" so that Claim 3 depends only on Claim 1.

Please cancel Claim 17 and substitute new Claim 19, written below.

-- 19. (New) A method for the treatment and/or prevention of a clinical condition for which selective agonism or antagonism of 5-HT₆ receptors is indicated comprising administering to a patient in need of such treatment an effective amount of a compound, or a pharmaceutically acceptable salt or prodrug thereof, having a structure in accordance with Formula I as defined in Claim 13. --

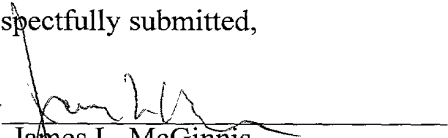
REMARKS

The claims have been amended to correct obvious spelling errors and to eliminate multiple dependent claims. Claim 17 was canceled and rewritten as a method of use claim. None of these amendments constitute new matter.

Examination on the merits is respectfully requested. If the Examiner wishes to discuss any matter regarding this application, the Examiner is invited to telephone the undersigned.

Respectfully submitted,

By


James L. McGinnis
Reg. No. 34,387
Attorney for Applicant

MERCK & CO., Inc.
P.O. Box 2000
Rahway, New Jersey 07065-0907
(732) 594-0641

Date: September 9, 1999

09392406-090999

TITLE OF THE INVENTION

INDOLE AND INDOLINE DERIVATIVES AS 5-HT₆ SELECTIVE LIGANDS

FIELD OF THE INVENTION

The present invention relates to classes of indole derivatives which bind selectively to 5-HT₆ receptors, and hence are potentially useful in the treatment of a number of clinical conditions believed to be sensitive to the selective agonism or antagonism of the 5-HT₆ receptors. Certain of the compounds are novel.

BACKGROUND OF THE INVENTION

The actions of the neurotransmitter 5-hydroxytryptamine (5-HT) are mediated through a number of receptor families termed 5-HT₁, 5-HT₂, 5-HT₃, 5-HT₄, 5-HT₅, 5-HT₆, and 5-HT₇ (see D. Hoyer et al., *Pharmacol. Rev.*, 1994, **46**, 157-204). Although the functions of the 5-HT₅, 5-HT₆ and 5-HT₇ receptors are less well understood than the functions of the other 5-HT receptors, it is generally accepted that compounds which selectively interfere with 5-HT-mediated signal transduction are important novel drug targets. In particular, 5-HT₆ selective ligands have been identified as potentially useful in the treatment of certain CNS disorders such as Parkinson's disease, Huntingdon's disease, anxiety, depression, manic depression, psychosis, epilepsy, obsessive compulsive disorders, migraine, Alzheimers disease (enhancement of cognitive memory), sleep disorders, feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus. Such compounds are also expected to be of use in the treatment of certain GI (gastrointestinal) disorders such as IBS (Irritable Bowel Syndrome). (See WO98/27058, WO98/27081, Drug

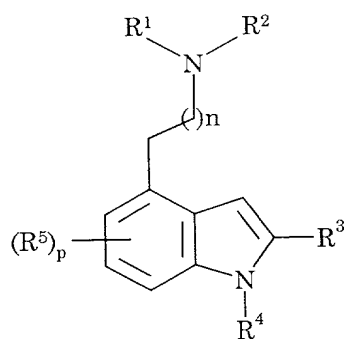
News Perspectives, 1997, **10**, 214 and A.J. Sleight et al., *Serotonin ID Research Alert*, 1997, **2**(3), 115-8).

A wide variety of 5-HT analogues incorporating an indole nucleus have been prepared and tested for pharmacological effects, but hitherto none has been shown to be a selective ligand for 5-HT₆ receptors. WO-A-98/27058 and WO-A-98/27081 disclose, respectively, sulphonamides and carboxamides which are 5-HT₆ receptor antagonists, but none of the compounds disclosed comprises an indole or indoline nucleus. Similarly, certain benzenesulphonamides of non-indole nature are disclosed as selective 5-HT₆ antagonists in EP-A-815861 and in *Br.J.Pharmacol.*, 1998, **124**, 556-562.

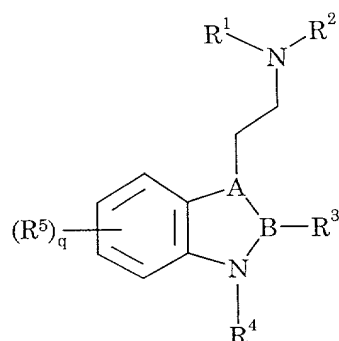
Many analogues of 5-HT are known, comprising a 1-acyl- or 1-arylsulphonyl-3-(2-aminoethyl) indole nucleus (see, for example, US Patents Nos. 3,481,953 and 3,489,429). Fused-ring analogues, such as trans-4-dimethylamino-1-(4-methylbenzenesulphonyl)-1,3,4,5-tetrahydrobenz[cd]indol-5-ol, are also known (*J.Chem.Soc., Perkin Trans.I*, 1973, 438-42). Analogues comprising a 4-(2-N,N-dialkylaminoethyl)indole nucleus, unsubstituted in the 1-position, have been shown to be dopamine agonists (*Eur. J. Med. Chem.*, 1991, **26**, 473-5; *J. Med. Chem.*, 1984, **27**, 386-9). However, the 1-substituted derivatives disclosed herein are believed to be novel.

SUMMARY OF THE INVENTION

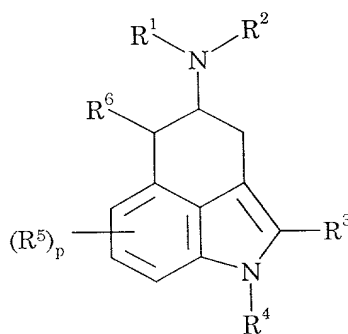
The present invention, in a first aspect, provides the use of a compound, or a pharmaceutically acceptable salt or prodrug thereof, for the manufacture of a pharmaceutical composition for the treatment and/or prevention of clinical conditions for which selective agonism or antagonism of 5-HT₆ receptors is indicated, said compound being an indole or indoline derivative having a structure in accordance with Formula I, II or III:



(I)



(II)



(III)

wherein

n is 1 or 2;

p is 0,1,2 or 3;

q is 0,1,2,3 or 4;

R¹ and R² independently represent hydrogen, C₁₋₆ alkyl or aryl

(C₁₋₆)alkyl, or together represent the atoms necessary to complete a

heterocycloalkyl group comprising the nitrogen atom to which R¹ and R² are attached;

R³ represents hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl(C₁₋₆)alkyl, aryl, heteroaryl, arylcarbonyl, heteroarylcarbonyl or C₁₋₆ alkylcarbonyl;

R⁴ represents arylsulphonyl, heteroarylsulphonyl, C₁₋₆ alkylsulphonyl, di(C₁₋₆)alkylaminosulphonyl, arylcarbonyl, C₁₋₆ alkylcarbonyl, heteroarylcarbonyl or C₁₋₆ alkoxy carbonyl;

each R⁵ independently represents hydroxy, C₁₋₆ alkoxy, aryl(C₁₋₆)alkoxy, nitrile or halogen;

R⁶ represents hydrogen, hydroxy or C₁₋₆ alkoxy; and

-A-B- represents -C=C- or -CH-CH-.

Also in its first aspect, the invention further provides a method for the treatment and/or prevention of clinical conditions for which selective agonism or antagonism of 5-HT₆ receptors is indicated comprising administering to a patient in need of such treatment an effective amount of a compound in accordance with Formulae I, II or III, or a pharmaceutically acceptable salt or a prodrug thereof.

Compounds of Formula I wherein n, p, and R¹ - R⁵ are defined as before, and salts and prodrugs thereof, are novel and constitute a second aspect of the invention.

In its second aspect, the invention also provides a pharmaceutical composition comprising one or more compounds of Formula I, or pharmaceutically acceptable salts or prodrugs thereof, in association with a pharmaceutically-acceptable carrier.

Also in its second aspect, the invention further provides a compound of Formula I or a pharmaceutically acceptable salt or a prodrug thereof for use in therapy.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of Formulae I-III are selective ligands for 5-HT₆ receptors, having a 5-HT₆ receptor (rat or human) binding affinity (K_i), when measured in cell lines expressing cloned recombinant 5-HT₆ receptors, of less than 1μM, typically less than 100nM, and in preferred embodiments less than 10nM, and having a selective affinity for 5-HT₆

receptors relative to 5-HT₅ and/or 5-HT₇ receptors of at least 3-fold, typically at least 10-fold, and in preferred embodiments at least 100-fold.

In Formulae I-III, one or more substituents may be present on any alkyl or aryl group represented by any of R¹ - R⁵, or on any alkyl or aryl moiety of a group represented by any of R¹ - R⁵. Preferred substituents include C₁₋₆ alkyl, halogen, hydroxy and C₁₋₆ alkoxy.

As used herein, the expression “C₁₋₆ alkyl” includes methyl and ethyl groups, and straight-chained, branched or cyclic propyl, butyl, pentyl and hexyl groups. Particular alkyl groups are methyl, ethyl, *n*-propyl, isopropyl and *tert*-butyl. Derived expressions such as “C₁₋₆ alkoxy”, “C₁₋₆ alkylthio” and “C₁₋₆ alkylamino” are to be construed accordingly.

The expression “C₂₋₆ alkenyl” as used herein refers to straight-chained and branched alkenyl groups containing from 2 to 6 carbon atoms. Typical examples include vinyl, allyl, dimethylallyl and butenyl groups.

15 The expression “C₂₋₆ alkynyl” as used herein refers to straight-chained and branched alkynyl groups containing from 2 to 6 carbon atoms. Typical examples include ethynyl and propargyl groups.

Typical aryl groups include phenyl and naphthyl.

The expression “aryl(C₁₋₆)alkyl” as used herein includes benzyl,
 20 phenylethyl, phenylpropyl and naphthylmethyl.

Suitable heterocycloalkyl groups include azetidiny, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl groups.

Suitable heteroaryl groups include pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl, pyrazinyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, pyrrolyl, indolyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl and tetrazolyl groups.

The term “halogen” as used herein includes fluorine, chlorine, bromine and iodine, especially chlorine or fluorine.

30 For use in medicine, the salts of the compounds of Formulae I-III
will be pharmaceutically acceptable salts. Other salts may, however, be

useful in the preparation of the compounds of Formulae I-III or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of Formulae I-III include acid addition salts which may, for example, be formed by mixing a solution of the compound

5 according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid.

Furthermore, where the compounds of Formulae I-III carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include

10 alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The present invention includes within its scope the use of prodrugs of the compounds of Formulae I-III above. In general, such prodrugs will be functional derivatives of the compounds of Formulae I-III which are readily convertible *in vivo* into the required compounds of Formulae I-III. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in *Design of Prodrugs*, ed.

15 H. Bundgaard, Elsevier, 1985.

Certain compounds according to the present invention may be capable of existing as tautomeric forms. It is to be understood that all possible tautomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof in any proportion

25 are encompassed within the scope of the present invention.

30

In Formulae I-III, suitable separate identities for R¹ and R² include hydrogen, methyl, ethyl, propyl and benzyl, and suitable identities for R¹ and R² in combination include pyrrolidinyl, piperidinyl, piperazinyl, 4-methylpiperazinyl and morpholinyl.

5 Suitable identities for R^3 include hydrogen, methyl, ethyl, benzyl,
allyl, propargyl, benzoyl, phenyl, thienyl and furoyl.

Suitable identities for R⁴ include benzenesulphonyl, naphthalene-2-sulphonyl, o-, m- or p-toluenesulphonyl, o-, m- or p-chlorobenzenesulphonyl, o-, m- or p-methoxybenzenesulphonyl, methanesulphonyl, dimethylaminosulphonyl, thienylsulphonyl, benzoyl, acetyl, furoyl and *tert*-butoxycarbonyl.

Suitable identities for R⁵ include hydroxy, methoxy, ethoxy, propoxy, benzyloxy, nitrile, fluorine, chlorine and bromine. Preferably, there is no more than one R⁵ substituent (i.e. p and q are 0 or 1), and when a single R⁵ substituent is present, it is preferably in the para-position relative to the indole nitrogen.

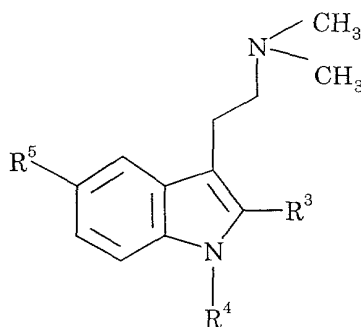
In the compounds of Formula I, p is preferably zero; R¹ and R² are preferably identical and represent hydrogen or methyl; R³ preferably represents hydrogen or benzoyl; and R⁴ preferably represents arylsulphonyl or dimethylaminosulphonyl. Examples of specific compounds in accordance with Formula I include:

2-[1-(benzenesulphonyl)-1*H*-indol-4-yl]ethylamine;
N,N-dimethyl 2-[1-(benzenesulphonyl)-1*H*-indol-4-yl]ethylamine;
N,N-dimethyl 2-[1-(dimethylamino)sulphonyl-1*H*-indol-4-yl]ethylamine;
25 *N,N*-dimethyl 3-[1-(benzenesulphonyl)-1*H*-indol-4-yl]propylamine; and
N,N-dimethyl 2-[1-(benzenesulphonyl)-2-benzoyl-1*H*-indol-4-yl]
ethylamine.

In the compounds of Formula II, preferably R¹ and R² are identical and represent hydrogen or methyl, or together complete a pyrrolidinyl, piperidinyl, piperazinyl or 4-methylpiperazinyl ring; R³ preferably represents hydrogen or methyl; R⁴ preferably represents arylsulphonyl.

thienylsulphonyl, benzoyl or *tert*-butoxycarbonyl; R⁵ preferably represents hydroxy, methoxy, benzyloxy or nitrile; and q is zero or 1.

A sub-class of compounds in accordance with Formula II is defined by Formula II(a):



(II(a))

where R³, R⁴ and R⁵ have the same meanings as before.

Specific examples of compounds in accordance with Formula II(a) include:-

N,N-dimethyl 2-[1-(benzenesulphonyl)-5-methoxy-1*H*-indol-3-yl]ethylamine;

N,N-dimethyl 2-[5-methoxy-1-(4-methylbenzenesulphonyl)-1*H*-indol-3-yl]ethylamine;

N,N-dimethyl 2-[1-(4-chlorobenzenesulphonyl)-5-methoxy-1*H*-indol-3-yl]ethylamine;

N,N-dimethyl 2-[1-(3-chlorobenzenesulphonyl)-5-methoxy-1*H*-indol-3-yl]ethylamine;

N,N-dimethyl 2-[5-methoxy-1-(2-naphthalenesulphonyl)-1*H*-indol-3-yl]ethylamine;

N,N-dimethyl 2-[5-methoxy-1-(4-methoxybenzenesulphonyl)-1*H*-indol-3-yl]ethylamine;

N,N-dimethyl 2-[1-(2-chlorobenzenesulphonyl)-5-methoxy-1*H*-indol-3-yl]ethylamine;

N,N-dimethyl 2-(1-benzoyl-5-methoxy-1*H*-indol-3-yl)ethylamine;

N,N-dimethyl 2-[5-methoxy-1-(2-thiophenesulphonyl)-1*H*-indol-3-yl]ethylamine;

N,N-dimethyl 2-(1-benzenesulphonyl-5-methoxy-2-methyl-1*H*-indol-3-yl)ethylamine;

N,N-dimethyl 2-(1-benzenesulphonyl-1*H*-indol-3-yl)ethylamine;

N,N-dimethyl 2-(1-methylsulphonyl-1*H*-indol-3-yl)ethylamine;

N,N-dimethyl 2-(5-methoxy-1-methylsulphonyl-1*H*-indol-3-yl)ethylamine;

[3-(2-dimethylamino-ethyl)-5-hydroxy-1*H*-indol-1-yl]phenylmethanone;

3-(2-dimethylamino-ethyl)-5-hydroxy-1*H*-indole-1-carboxylic acid *tert*-butyl ester;

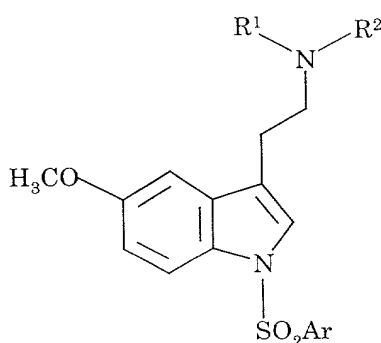
N,N-dimethyl 2-(1-benzenesulphonyl-5-benzyloxy-1*H*-indol-3-yl)ethylamine;

N,N-dimethyl 2-(1-benzenesulphonyl-5-hydroxy-1*H*-indol-3-yl)ethylamine;

and

N,N-dimethyl 2-(1-benzenesulphonyl-5-cyano-1*H*-indol-3-yl)ethylamine.

A further sub-class of compounds in accordance with Formula II is defined by Formula II(b):



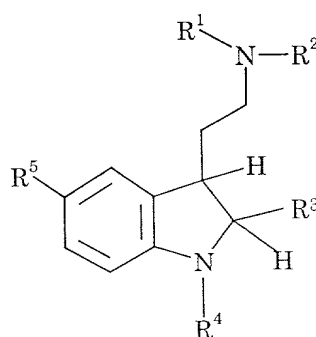
(II(b))

where R¹ and R² have the same meanings as before, and Ar represents an aryl group.

Specific examples of compounds in accordance with Formula II(b) include:

- 2-[1-(benzenesulphonyl)-5-methoxy-1*H*-indol-3-yl]ethylamine;
1-benzenesulphonyl-5-methoxy-3-[(2-pyrrolidin-1-yl)ethyl]-1*H*-indole;
5 1-benzenesulphonyl-5-methoxy-3-[(2-piperidin-1-yl)ethyl]-1*H*-indole; and
1-benzenesulphonyl-5-methoxy-3-[(2-piperazin-1-yl)ethyl]-1*H*-indole.

A third sub-class of compounds in accordance with Formula II is defined by Formula II(c):



(II(c))

- 10 where R¹ - R⁵ have the same meanings as before.

Specific examples of compounds in accordance with Formula II(c) include:

N,N-dimethyl 2-(1-benzenesulphonyl-5-methoxy-2,3-dihydro-1*H*-indol-3-yl)ethylamine.

- 15 In the compounds of Formula III, R¹ and R² are preferably identical and represent hydrogen or methyl; R³ preferably represents hydrogen; R⁴ preferably represents arylsulphonyl, especially *p*-toluenesulphonyl; R⁶ preferably represents hydroxy or methoxy; and *p* is preferably zero.

Specific examples of compounds in accordance with Formula III include:

- 20 *trans*-4-dimethylamino-1-(4-methylbenzenesulphonyl)-1,3,4,5-tetrahydro-benz[*cd*]indol-5-ol; and
4-dimethylamino-5-methoxy-1-(4-methylbenzenesulphonyl)-1,3,4,5-tetrahydro-benz[*cd*]indole.

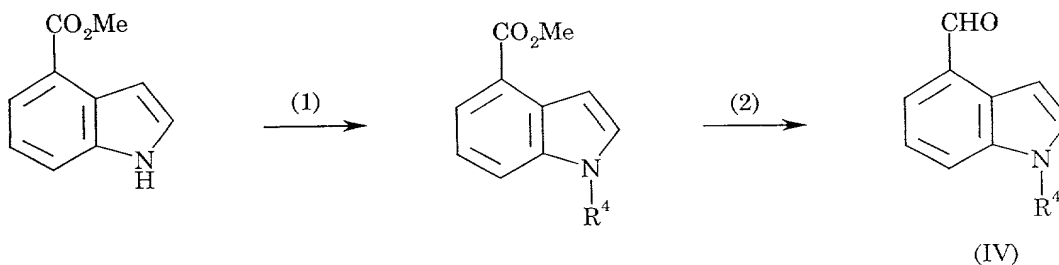
5 The invention also provides or uses pharmaceutical compositions comprising one or more compounds of Formulae I-III in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Typical unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets or pills of the pharmaceutical composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such

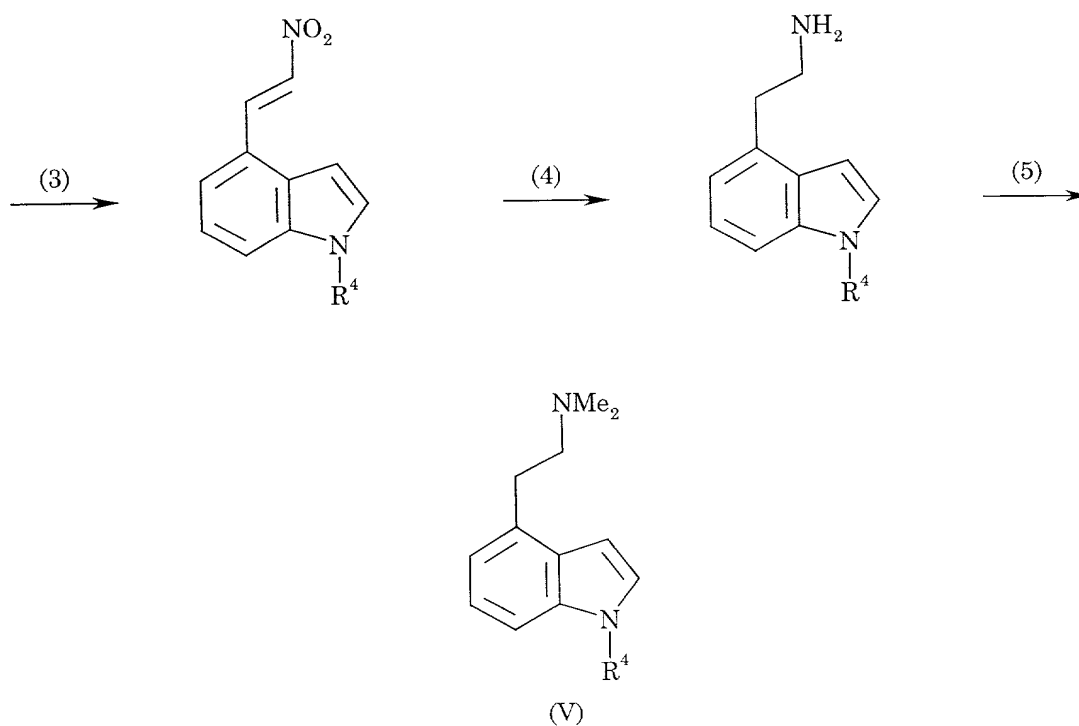
materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the pharmaceutical compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

In the treatment of the relevant clinical conditions, such as depression, Alzheimer's disease, Parkinson's disease and schizophrenia, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

A representative approach to the preparation of compounds of Formula I in which $n=1$ is illustrated in the following reaction scheme, in which the starting material (methyl indole-4-carboxylate) is prepared as described in J. Org. Chem., 1980, 45, 3350.

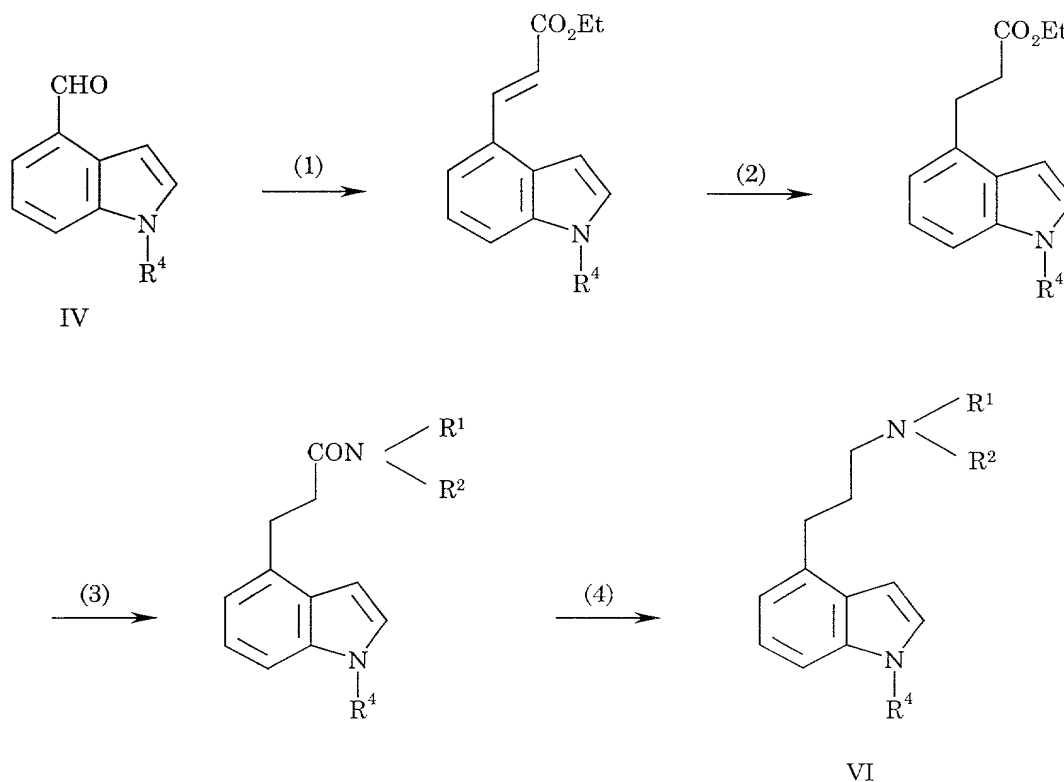




5 In step (1), reaction of the indole derivative with R⁴Cl in the presence of base introduces the desired R⁴- substituent in the 1-position (where R⁴ has the same definition as before). Alternatively, and in particular when R⁴ represents *tert*-alkoxycarbonyl, this step may be carried out last. In step (2), the methyl ester is first reduced to the corresponding hydroxymethyl derivative, e.g. by means of diisobutyl aluminium hydride, then oxidised to
10 the aldehyde IV using manganese (IV) oxide. In step (3), base-catalysed condensation of the aldehyde with nitromethane affords the 2-nitroethenyl derivative, which may be reduced (e.g. by zinc amalgam) to the 2-aminoethyl derivative (step (4)). If desired, mono- or dialkylation of the
15 primary amino group may be carried out by standard methods. The preferred dimethylamino derivatives (V) are most conveniently prepared by reductive alkylation of the primary amino with formaldehyde in the presence of sodium cyanoborohydride (step (5)).

The above-described indole-4-carboxaldehyde derivatives (IV) are
20 suitable starting materials for the preparation of compounds of Formula I

in which $n=2$, as shown in the following reaction scheme; where R^1 , R^2 and R^4 have the same meanings as before:

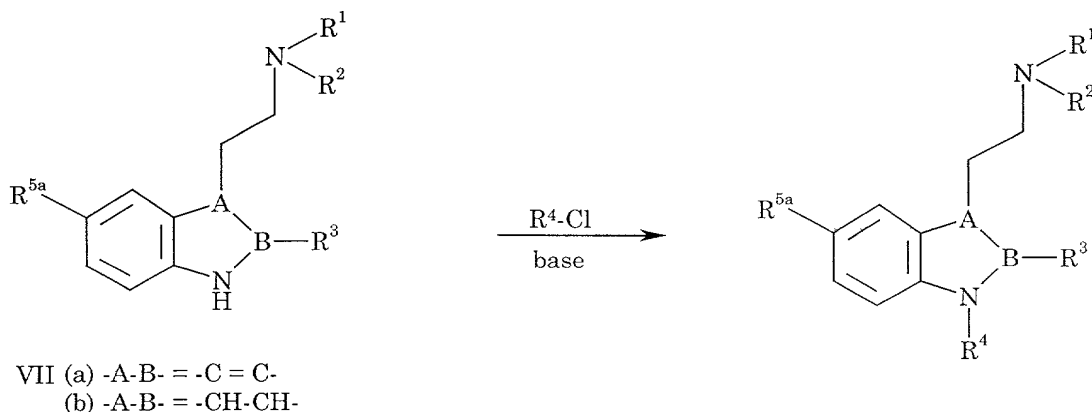


5

In step (1), reaction between the aldehyde (IV) and (carbethoxymethylene) triphenyl phosphorane provides the ethyl ester of the acrylic acid derivative, which is subsequently reduced by catalytic hydrogenation over Pd/C to the corresponding propionic ethyl ester in step (2). In step (3), reaction of the ester with R^1R^2NH provides the corresponding amide, which is then reduced to the amine (VI) by lithium aluminium hydride (step (4)). Alternatively, the same sequence of reactions may be performed on the corresponding N-unsubstituted indoles, with attachment of the R^4 group via reaction with R^4-Cl as a final step. This is preferable when R^4 represents alkylcarbonyl, *tert*-alkoxycarbonyl, arylcarbonyl, or heteroarylcarbonyl.

Compounds of Formula I in which R^3 represents alkyl, aryl or arylalkyl may be prepared by the routes shown above, but starting from the appropriate 2-substituted analogue of methyl indole-4-carboxylate.

Compounds of Formula II in which R^5 is other than OH may be prepared from the intermediates VII(a) and VII(b) as shown in the following reaction scheme:

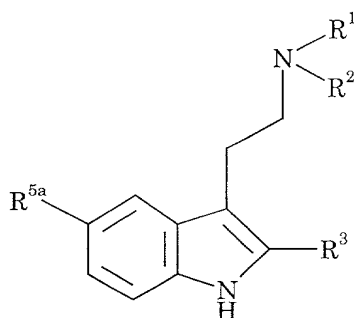


where R^1 , R^2 , R^3 and R^4 have the same meanings as before, and R^{5a} represents any group represented by R^5 except hydroxy.

In the event that either or both of R^1 and R^2 represents hydrogen, it is necessary to protect the exocyclic amino group as the t-butoxycarbonyl (Boc) derivative prior to functionalising the ring nitrogen, the Boc group being subsequently cleaved under acid conditions.

Compounds of Formula II in which R^5 represents hydroxy may be prepared by hydrogenolysis of the corresponding compounds in which R^5 represents benzyloxy.

The intermediates VII(b) in which -A-B- represents -CH-CH- may be prepared by catalytic hydrogenation of the intermediates VII(a) in which -A-B- represents -C=C-. Thus, the compounds VII(a):

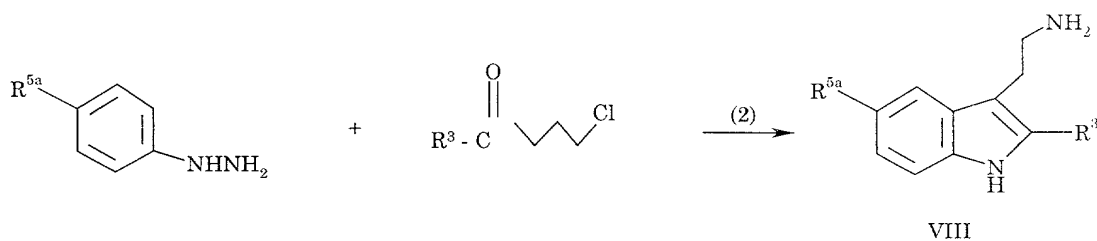


VII (a)

where R¹, R², R^{5a} and R³ have the same meanings as before, are key intermediates in the preparation of compounds of Formula II.

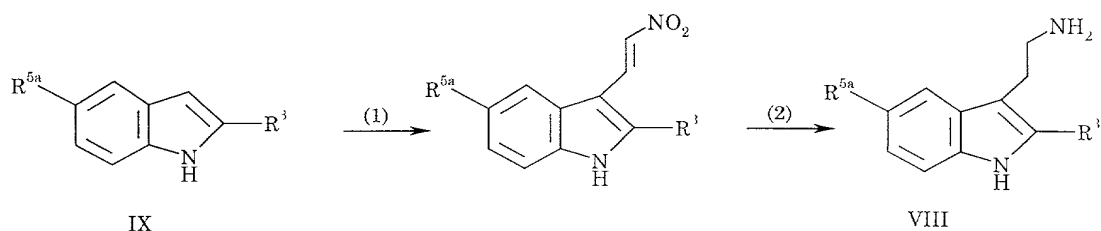
The compound of Formula VII(a) in which R¹ and R² represent methyl, R^{5a} represents methoxy, and R³ represents hydrogen is 5-methoxy-N,N-dimethyltryptamine, available commercially from Sigma, and is the preferred starting material for many of the compounds of Formula II.

Other compounds in accordance with Formula VII(a) may be prepared by a variety of routes, such as:



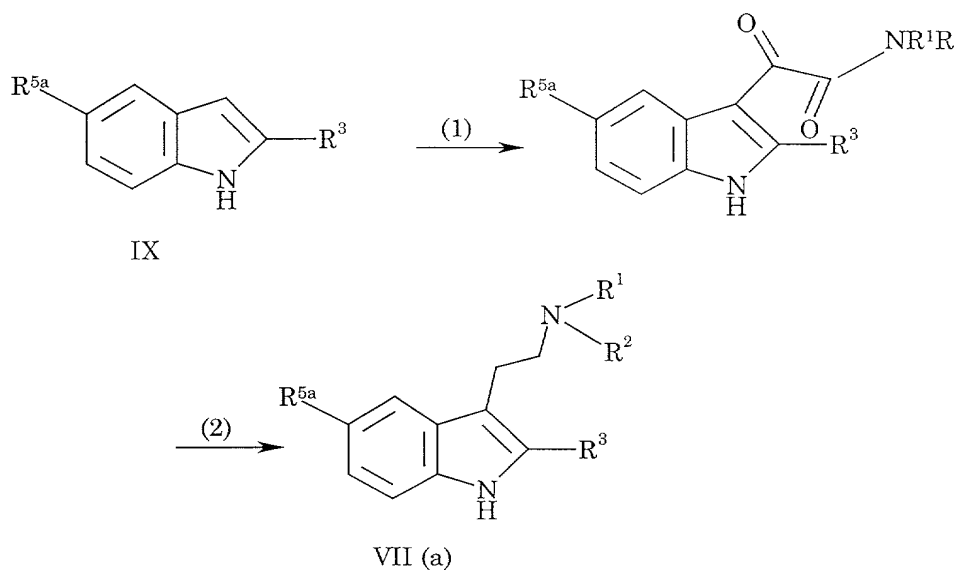
where R^{5a} and R³ have the same meanings as before. The reaction involves the well-known Fischer-indole cyclisation, with in situ substitution of the chlorine by amino (see J. Med. Chem., 1994, **37**, 3023). If required, the primary amino group of VIII may be reductively alkylated by reaction with formaldehyde in the presence of sodium cyanoborohydride to provide the compounds VII(a) in which R¹ = R² = methyl.

An alternative route to the compounds VIII is depicted in the following reaction scheme:



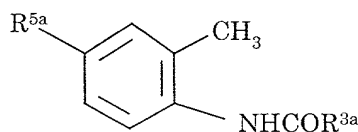
where R^{5a} and R^3 have the same meanings as before. Step (1) involves
5 coupling of the indole IX with 1-dimethylamino-2-nitroethylene in the
presence of trifluoroacetic acid, and step (2) involves reduction with
lithium aluminium hydride. Both steps are described in J. Med. Chem.,
1993, **36**, 4069.

A further route to the compounds VII(a), also starting from the
10 indoles IX, is depicted in the following reaction scheme:



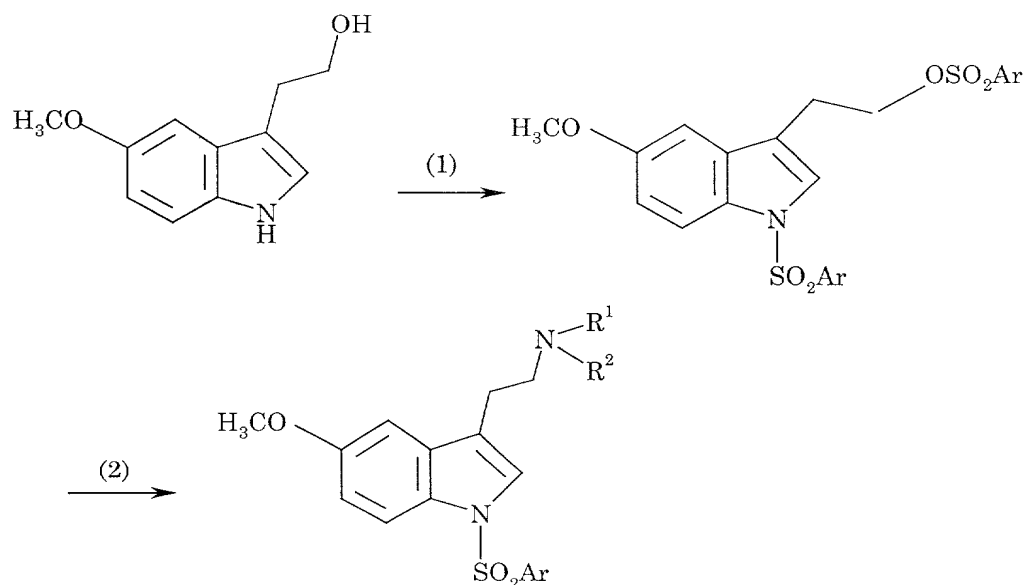
where R^1 , R^2 , R^3 and R^{5a} have the same meanings as before. Step (1)
15 involves reaction of the indoles IX with oxalyl chloride, followed by
condensation with an amine R^1R^2NH . Step (2) involves reduction by
lithium aluminium hydride of the α -ketoamide group.

The indoles IX may be prepared by the standard Fischer-indole synthesis, or more conveniently (when R³ does not represent hydrogen) by treatment of the N-acyl derivatives X with n-butyllithium:



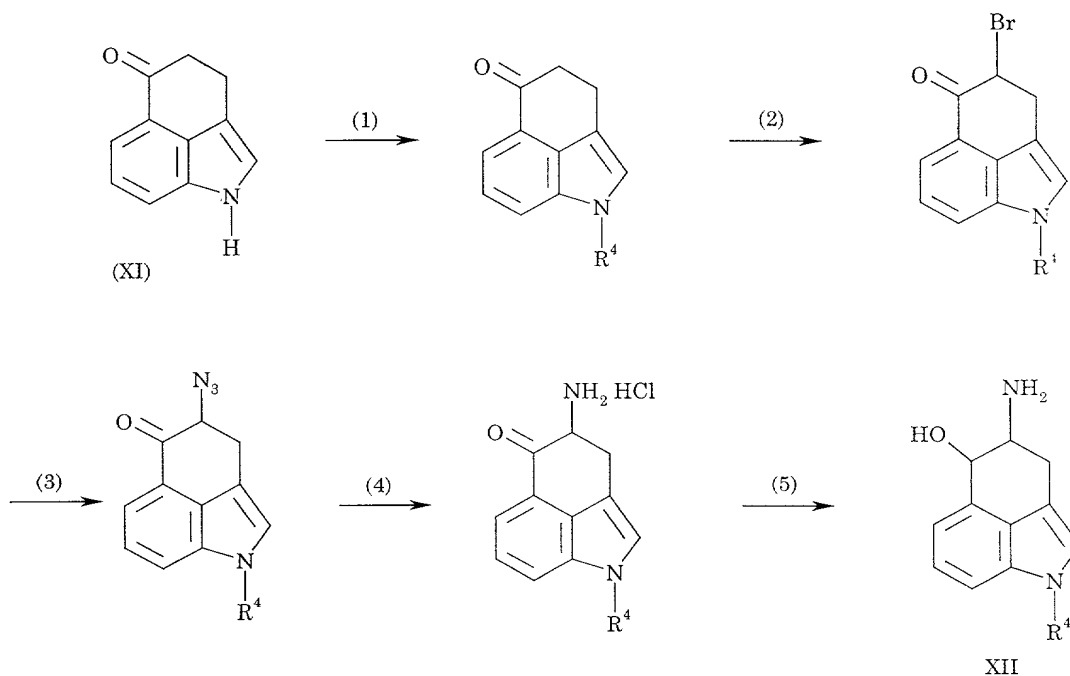
where R^{5a} is defined as before and R^{3a} represents any group represented by R³ except hydrogen (see J. Med. Chem., 1993, 36, 4069).

A preferred route to the compounds of Formula II(b) is shown in the following reaction scheme, in which R¹, R² and Ar have the same meanings as before, and the starting material (5-methoxytryptophol) is commercially available from Sigma.



Step (1) involves reaction of 5-methoxytryptophol with at least two equivalents of arylsulphonyl chloride in the presence of base. Step (2) involves reaction of the resulting arylsulphonate ester with R^1R^2NH so as to cause nucleophilic displacement of the arylsulphonate group.

5 Representative compounds of Formula III may be prepared by the route shown in the following reaction scheme, in which R^4 has the same meaning as before, and the ketone XI is prepared as described in J. Chem. Soc. Perkin Trans. I, 1972, 1121:



10

In step (1), reaction of XI with R^4-Cl in the presence of base affords the N-substituted derivative, which is then converted (step (2)) to the α -bromoketone by treatment with phenyl trimethyl ammonium bromide perbromide. Nucleophilic displacement of the bromine atom is effected by reaction with sodium azide in DMF (step (3)), and catalytic hydrogenation of the azide over Pd/C (step (4)) affords the corresponding α -aminoketone. Finally, the ketone is reduced by reaction with sodium borohydride (step (5)) to provide the aminoalcohol XII as a racemic mixture. If necessary,

15

the primary amino group of XII may be reductively alkylated (e.g. by hydrogenation over Pd/C in the presence of formaldehyde, acetaldehyde etc.) to form the corresponding N,N-dialkyl derivatives. Additionally, or alternatively, the hydroxyl group of XII may be alkylated by the standard methods of ether synthesis.

It will be understood that any compound of Formula I, II or III initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further compound of Formula I, II or III respectively by techniques known from the art. For example, a compound of Formula I, II or III in which R^3 represents hydrogen may be reacted with tert-butyllithium to provide the 2-lithio derivative, which may then be reacted with an alkyl, aryl or heteroaryl aldehyde to form a secondary alcohol, which in turn may be oxidised using manganese IV oxide to give the compounds of Formula I, II or III in which R^3 represents alkylcarbonyl, arylcarbonyl or heteroarylcarbonyl. Alternatively, the aforementioned secondary alcohols formed by the reaction of the lithio derivative with an alkyl aldehyde may be subjected to dehydrative elimination to form compounds of Formula I, II or III in which R^3 represents alkenyl. Furthermore, compounds of Formula I, II or III in which either or both of R^1 and R^2 represents hydrogen may be alkylated by any of the standard techniques of N-alkylation to provide the corresponding compounds of Formulae I-III in which either or both of R^1 and R^2 represents alkyl. Suitable techniques of N-alkylation include treatment with the appropriate aldehyde or ketone in the presence of sodium cyanoborohydride. Additionally, a compound of Formula I, II or III in which R^5 represents benzyloxy may be converted by catalytic hydrogenation to the corresponding compound of Formula I, II or III in which R^5 represents hydroxy, which in turn may be alkylated by standard methods to provide a corresponding compound in which R^5 represents alkoxy.

Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by standard techniques such as preparative HPLC, or the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-*p*-toluoyl-d-tartaric acid and/or (+)-di-*p*-toluoyl-l-tartaric acid, followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

EXAMPLE 1

2-[1-(Benzenesulphonyl)-1*H*-indol-4-yl]ethylamine Hydrogen Oxalate

5

a) Methyl 1-(benzenesulphonyl)-1*H*-indole-4-carboxylate

A mixture of methyl indole-4-carboxylate (*J. Org. Chem.* **1980**, *45*, 3350) (5.0 g, 28.5 mmol), benzenesulphonyl chloride (10.1 g, 57.1 mmol) and anhydrous potassium carbonate (15.78 g, 114 mmol) in butan-3-one
10 (150 ml) was refluxed under nitrogen for 15 hours. Additional benzenesulphonyl chloride (10.1 g) and anhydrous potassium carbonate (10.1 g) were added and refluxing was continued for 5 hours. The mixture was diluted with water (300 ml) and extracted with diethyl ether (3 x 300 ml). The combined organic solutions were dried (MgSO₄) and concentrated
15 to give a white solid which was recrystallised from ethanol (6.35g, 72%); δ_{H} (360MHz, CDCl₃), 8.21 (1H, d, J=8.3Hz, Ar-H), 7.96 (1H, dd, J=8.1 and 0.7Hz, Ar-H), 7.87-7.84 (2H, m, Ar-H), 7.69 (1H, d, J=3.7Hz, Ar-H), 7.56-7.33 (5H, m, Ar-H), 3.94 (3H, s, -OMe); m/z (CI) 316 (M⁺+1).

b) 1-(Benzenesulphonyl)-1*H*-indole-4-carboxaldehyde

To a cooled (-70°C) and stirred solution of methyl 1-(benzenesulphonyl)-1*H*-indole-4-carboxylate (4.5 g, 14.3 mmol) in anhydrous diethyl ether (50 ml) was added diisobutylaluminium hydride (1M in toluene; 37 ml) over 30 minutes, under a nitrogen atmosphere.
25 After being stirred at -70°C for 3 hours, excess diisobutylaluminium hydride was destroyed by dropwise addition of methanol (3 ml) and the mixture was allowed to warm to room temperature. 5% Aqueous citric acid (100 ml) was added, products were extracted with ethyl acetate (3 x 100 ml) and the organic phases were dried (MgSO₄) and concentrated.
30 Flash chromatography of the residue (silica gel, hexane-ethyl acetate,

50:50) gave 2.6 g (63%) of the intermediate 1-(benzenesulphonyl)-1*H*-indole-4-methanol as a thick colourless oil.

To a solution of the above alcohol (2.5 g) in anhydrous dichloromethane (200 ml) was added activated manganese (IV) oxide (9 g) and the resulting mixture was stirred for 15 hours at room temperature, under a nitrogen atmosphere. The manganese residues were removed by filtration, washed with chloroform and the filtrate was concentrated under vacuum to give 1.96 g (79%) of the title compound as a white solid; δ_{H} (250MHz, CDCl_3) 7.42-7.56 (5H, m), 7.72-7.77 (2H, m), 7.86-7.90 (2H, m), 8.28 (1H, d, $J=8.25\text{Hz}$); 10.18 (1H, s); m/z (EI) 285 (M^+). (Found: m/z 285.0444. $\text{C}_{15}\text{H}_{11}\text{NO}_3\text{S}$ requires: m/z 285.0460).

c) 1-(Benzenesulphonyl)-4-(2-nitrovinyl)-1*H*-indole

To a solution of 1-benzenesulphonyl-1*H*-indole-4-carboxaldehyde (1.9 g, 6.6 mmol) in nitromethane (12 ml) was added ammonium acetate (205 mg, 2.7 mmol) and the resulting mixture was refluxed for 2 hours. Water (50 ml) was added and products were extracted with ethyl acetate (2 x 100 ml). The combined organic phases were washed with brine (1 x 30 ml), dried (MgSO_4) and concentrated. Flash chromatography (silica gel, dichloromethane-hexane, 75:25) of the residue gave 1.95g (90%) of the title compound as a pale yellow solid; δ_{H} (250MHz, CDCl_3) 8.27 (1H, d, $J=13.7\text{Hz}$), 8.14 (1H, d, $J=8.2\text{Hz}$), 7.92-7.87 (2H, m), 7.75 (1H, d, $J=3.7\text{Hz}$), 7.65 (1H, d, $J=13.7\text{Hz}$), 7.62-7.34 (5H, m), 6.89 (1H, dd, $J=3.7$ and 0.9Hz); m/z (CI) 299 (M^++1).

d) 2-[1-(Benzenesulphonyl)-1*H*-indol-4-yl]ethylamine Hydrogen Oxalate

Zinc amalgam was prepared by mixing zinc dust (6 g) and mercury (II) chloride (600 mg) in a mixture of water (6 ml) and concentrated hydrochloric acid (300 μl) and stirring at room temperature for 10 minutes. The aqueous phase was decanted off and the amalgam was then covered with methanol.

To a cooled (0°C) and stirred solution of 1-(benzenesulphonyl)-4-(2-nitrovinyl)-1*H*-indole (1.9 g) in a mixture of methanol (35 ml) and concentrated hydrochloric acid (20 ml) was added portionwise, over 30 minutes, the zinc amalgam prepared above. The mixture was stirred at 5 0°C for a further 30 minutes and at room temperature for 2 hours before the solvent was decanted off and evaporated under vacuum. The remaining residue was partitioned between 1M aqueous ammonia (50 ml) and diethyl ether (75 ml) and the aqueous phase was re-extracted with diethyl ether (2 x 75 ml). The combined ethereal solutions were dried 10 (Na₂SO₄) and concentrated. Flash chromatography of the residue (silica gel, dichloromethane-methanol-ammonia, 40:8:1) gave 950 mg of the title compound free base as a thick colourless oil; δ_H (250MHZ, CDCl₃), 7.86 (3H, d); 7.60-7.36 (4H, m), 7.20 (1H, t), 7.04 (1H, d), 6.78 (1H, d), 3.06 (4H, s); m/z (EI) 301 (M⁺+1).

EXAMPLE 2

N,N-Dimethyl 2-[1-(benzenesulphonyl)-1*H*-indol-4-yl]ethylamine

Hydrogen oxalate

20 A solution of aqueous formaldehyde (38% w/v; 790 μ l) in methanol (10 ml) was added dropwise to a cooled (0°C) and stirred mixture of 2-[1-(benzenesulphonyl)-1*H*-indol-4-yl]ethylamine (750 mg), sodium cyanoborohydride (345 mg) and glacial acetic acid (715 μ l) in methanol (30 ml). The mixture was then allowed to warm to room temperature and it 25 was stirred for 1 hour before saturated aqueous potassium carbonate (20 ml) was added and the methanol was removed under vacuum. The remaining residue was diluted with water (20 ml) and products were extracted with ethyl acetate (3 x 50 ml). The combined organic solutions were washed with brine (1 x 30 ml), dried (MgSO₄) and concentrated. 30 Flash chromatography of the residue (silica gel, dichloromethane-methanol, 90:10) gave 550 mg (67%) of the title compound as a colourless

thick oil. The oxalate salt was prepared and recrystallised from isopropanol-ether; mp 192-195°C; δ_{H} (360MHz, D₂O) 7.93-7.89 (3H, m), 7.77 (1H, d, J=3.8Hz), 7.60 (1H, t, J=7.6Hz), 7.50-7.45 (2H, m), 7.35 (1H, t, J=8.2Hz), 7.19 (1H, d, J=7.5Hz), 6.91 (1H, d, J=3.9Hz), 3.43-3.37 (2H, m), 3.28-3.22 (2H, m), 2.89 (6H, s); m/z (EI) 329 (M⁺+1). (Found: C, 56.73; H, 5.26; N, 6.65. C₁₈H₂₀N₂O₂S.1.0 C₂H₂O₄.0.2 H₂O requires: C, 56.91; H, 5.35; N, 6.64%). (Found: m/z 328.1259. C₁₈H₂₀N₂O₂S requires: m/z 328.1246).

EXAMPLE 3

N,N-Dimethyl 2-[1-(dimethylamino)sulphonyl-1H-indol-4-yl]ethylamine. Hydrogen Oxalate

The title compound was prepared from 4-[2-(dimethylamino)ethyl]-1H-indole (P.E. Persons et al., *Eur. J. Med. Chem.*, **1991**, *26*, 473-475) and N,N-dimethylaminosulphonyl chloride following a similar method to that described for Example 6. The oxalate salt was prepared from ethanol-diethyl ether; mp 153-155°C; δ_{H} (360MHz, DMSO-d₆) 7.78 (1H, d, J=8.6Hz), 7.70 (1H, d, J=3.6Hz), 7.30 (1H, t, J=7.6Hz), 7.15 (1H, d, J=7.3Hz), 6.98 (1H, d, J=3.6Hz), 3.23 (4H, s), 2.80 (6H, s), 2.79 (6H, s); m/z (EI) 296 (M⁺+1). (Found: C, 49.60; H, 5.89; N, 10.35. C₁₄H₂₁N₃O₂S.1.1 C₂H₂O₄ requires: C, 49.33; H, 5.93; N, 10.65%).

EXAMPLE 4

N,N-Dimethyl 3-[1-(benzenesulphonyl)-1H-indol-4-yl]propylamine. Hydrogen Oxalate

a) 3-[1-(Benzenesulphonyl)-1H-indol-4-yl]acrylic acid ethyl ester

A solution of 1-(benzenesulphonyl)-1H-indole-4-carboxaldehyde (2.0 g, 7 mmol) and (carbethoxymethylene)triphenylphosphorane (2.69 g, 7.7

mmol) in anhydrous dichloromethane (50 ml) was heated to reflux for 3 h under a nitrogen atmosphere. The reaction was concentrated and purified by dry flash chromatography (dichloromethane) to give the title compound as a colourless solid (2.49 g, 100%). δ_{H} (360MHz, CDCl_3), 1.34 (3H, t, $J=7.2\text{Hz}$), 4.27 (2H, q, $J=7.2\text{Hz}$), 6.51 (1H, d, $J=17.2\text{Hz}$), 6.94 (1H, d, $J=0.72\text{Hz}$), 7.32 (1H, t, $J=7.9\text{Hz}$), 7.43-7.67 (4H, m), 7.67 (1H, d, $J=3.6\text{Hz}$), 7.68-7.89 (2H, m), 7.94-8.03 (2H, m).

b) 3-[1-(Benzenesulphonyl)-1*H*-indol-4-yl]propionic acid ethyl ester

3-[1-(Benzenesulphonyl)-1*H*-indol-4-yl]acrylic acid ethyl ester (2.48 g, 6.98 mmol) was hydrogenated over 10% Pd-C (500 mg) in ethyl acetate-ethanol (4:1; 75 ml), under an atmosphere of hydrogen. The catalyst was removed by filtration after 4 h, and the solvents were removed to obtain the title compound as a colourless oil which crystallised on standing (2.47 g, 100%); δ_{H} (CDCl_3 , 360MHz) 1.10 (3H, t, $J=6.8\text{Hz}$), 2.57 (2H, t, $J=7.5\text{Hz}$), 3.06 (2H, t, $J=7.5\text{Hz}$), 4.02 (2H, q, $J=7.2\text{Hz}$), 6.66 (1H, d, $J=0.72\text{Hz}$), 6.98 (1H, d, $J=7.5\text{Hz}$), 7.14-7.18 (1H, m), 7.34-7.38 (2H, m), 7.43-7.48 (1H, m), 7.50 (1H, d, $J=3.96\text{Hz}$), 7.77-7.82 (3H, m).

c) *N,N*-Dimethyl-3-[1-(benzenesulphonyl)-1*H*-indol-4-yl]propionamide

Trimethylaluminium (1.4 ml, 2M solution in hexanes) was added to a suspension of dimethylamine hydrochloride (228 mg, 2.8 mmol) in 10 ml benzene. The reaction was allowed to stir for 1h before dropwise addition of a solution of 3-[1-(benzenesulphonyl)-1*H*-indol-4-yl]propionic acid ethyl ester (0.5g, 1.4 mmol) in benzene (10 ml). The reaction was heated at reflux for 18 h, allowed to cool and then quenched by addition of HCl (2N, 5 ml). The reaction was partitioned between H_2O -EtOAc. The organic phase was washed with brine, dried (MgSO_4), and concentrated to give the title compound as an oil which crystallised (527 mg, 100%); δ_{H} (CDCl_3 , 250MHz), 2.63 (2H, t, $J=7.5\text{Hz}$), 2.79 (2H, br s), 3.16 (2H, t, $J=8.5\text{Hz}$), 6.74

(1H, d, J=0.7Hz), 6.08 (1H, d, J=7.5Hz), 7.21-7.27 (1H, m), 7.41-7.58 (4H, m), 7.84-7.90 (3H, m).

d) *N,N*-Dimethyl 3-[1-(benzenesulphonyl)-1*H*-indol-4-yl]propylamine

5 Hydrogen Oxalate

A solution of the product from above (527 mg, 1.4 mmol) in 15 ml THF was treated dropwise with lithium aluminium hydride (1.4 ml, 1.0M THF) whilst stirring under a nitrogen atmosphere. The reaction was stirred for 5 h, and quenched with water (1 ml). The reaction was filtered
10 through a glass fibre pad, and the filtrate concentrated. The residue was partitioned between 2N NaOH-EtOAc. The organic phase was dried (Na₂SO₄), concentrated and purified by chromatography [CH₂Cl₂-MeOH-NH₄OH (95:5:0.5)] to give the title compound free base as an oil (2.75 mg, 50%). The oxalate salt was prepared in diethyl ether; mp 142-144°C.
15 (Found: C, 56.29; H, 5.06; N, 6.12. C₁₉H₂₀N₂O₃S. 1.3 C₂H₂O₄ requires C, 56.46; H, 5.40; N, 6.10). δ_H (d₆-DMSO, 250MHz) 1.8-2.0 (2H, m), 2.67 (6H, s), 2.78-2.84 (2H, m), 2.98-3.04 (2H, m), 6.97 (1H, d, J=3.75Hz), 7.11 (1H, d, J=7Hz), 7.29 (1H, t, J=7.5Hz), 7.11 (1H, d, J=7Hz), 7.29 (1H, t, J=7.5Hz), 7.57-7.73 (3H, m), 7.79-7.85 (2H, m), 7.98-9.01 (2H, m); *m/z*
20 (ES⁺) 343 (M⁺+1).

EXAMPLE 5

N,N-Dimethyl 2-[1-(benzenesulphonyl)-2-benzoyl-1*H*-indol-4-yl]ethylamine. Hydrogen oxalate
25

To a cooled (-78°C) and stirred solution of *N,N*-dimethyl 2-[1-(benzenesulphonyl)-1*H*-indol-4-yl]ethylamine (1.16 g, 3.6 mmol) in anhydrous tetrahydrofuran (8 ml) was added dropwise, under nitrogen, *tert*-butyllithium (1.7 M in pentane, 25 ml). The resulting solution was
30 stirred at -78°C for 30 minutes and then it was allowed to warm to 0°C over 1 h. After being re-cooled to -78°C, a solution of freshly distilled

benzaldehyde (415 mg, 3.9 mmol) in anhydrous tetrahydrofuran (4 ml) was added and the mixture was allowed to warm to room temperature over 3 h. The reaction was quenched by addition of water (20 ml) and products were extracted with ethyl acetate (2 x 75ml), dried (MgSO₄) and concentrated. Flash chromatography (silica gel, dichloromethane-ethanol, 90:10 to dichloromethane-methanol-ammonia, 60:8:1) of the residue gave 600 mg of [1-(benzenesulphonyl)-4-[2-(dimethylamino)ethyl]-1*H*-indol-2-yl]phenylmethanol as a white solid.

To a solution of the above alcohol (350 mg) in anhydrous dichloromethane (20 ml) was added activated manganese (IV) oxide (250 mg) and the resulting mixture was stirred vigorously at room temperature for 30 minutes. The manganese residues were filtered off, washed with dichloromethane and the filtrate was concentrated under vacuum. Flash chromatography of the residual oil (silica gel, dichloromethane-ethanol, 90:10 to dichloromethane-methanol-ammonia, 60:8:1) gave 330 mg of the title compound as a yellow oil. The hydrogen oxalate salt was prepared and recrystallised from isopropanol-diethyl ether; mp 154-156°C; δ_H (360MHz, d₆-DMSO) 8.03-7.93 (5H, m), 7.78-7.72 (2H, m), 7.68-7.59 (4H, m), 7.51-7.46 (2H, m), 7.26 (1H, d, J=7.4Hz), 3.16 (4H, s, -CH₂CH₂-), 2.73 (6H, s, -NMe₂). (Found: C, 61.70; H, 5.07; N, 5.33. C₂₅H₂₄N₂O₃S.1.0 C₂H₂O₄.0.2 H₂O requires: C, 61.66; H, 5.02; N, 5.33%).

EXAMPLE 6

N,N-Dimethyl 2-[1-(benzenesulphonyl)-5-methoxy-1*H*-indol-3-yl]ethylamine Hydrochloride

To a stirred two-phase mixture of 5-methoxy-*N,N*-dimethyl-tryptamine (2 g, 9.16 mmol) and tetrabutylammonium hydrogen sulphate (311 mg, 0.916 mmol) in dichloromethane (120 ml) and 50% aqueous sodium hydroxide (30 ml) was added benzenesulphonyl chloride (2.43 g, 13.74 mmol) over 30 minutes. The mixture was stirred at room

temperature for 20 minutes, diluted with ethyl acetate (250 ml) and water (125 ml), and the organic phase was decanted off, washed with brine (2 x 65 ml), dried (MgSO₄) and concentrated. Flash chromatography (silica gel, dichloromethane-methanol-ammonia, 95:5:0.5) of the residue afforded
5 3.166 g (96%) of the title compound free base as a thick oil which solidified on standing. The hydrogen chloride salt was prepared; mp 200-215°C (EtOH); δ_H (360MHz, DMSO-d₆) 10.82 (1H, br s), 7.92 (2H, dd, J=8.6 and 1.3Hz), 7.82 (1H, d, J=9.0Hz), 7.72-7.65 (2H, m), 7.58 (2H, t, J=7.5Hz), 7.26 (1H, d, J=2.5Hz), 6.98 (1H, dd, J=9.0 and 2.5Hz), 3.80 (3H, s), 3.36-
10 3.28 (2H, m), 3.16-3.28 (2H, m), 3.16-3.06 (2H, m), 2.81 (6H, s); m/z (ES) 359 (M⁺+1). (Found: C, 58.04; H, 5.97; N, 7.37. C₁₉H₂₂N₂SO₃.HCl requires: C, 57.79; H, 5.87; N, 7.09%).

EXAMPLE 7

15 *N,N*-Dimethyl 2-[5-methoxy-1-(4-methylbenzenesulphonyl)-1*H*-indol-3-yl]ethylamine Hydrochloride

Following a similar procedure to that described in Example 6, but using *p*-toluenesulphonyl chloride instead of benzenesulphonyl chloride,
20 the title compound was prepared in 72% yield as a white solid; mp 214-215°C; δ_H (360 MHz, *d*₆-DMSO) 2.32 (3H, s), 2.81 (6H, s), 3.08 (2H, m), 3.37 (2H, m), 3.79 (3H, s), 6.97 (1H, dd, J=9.0, 2.5 Hz), 7.23 (1H, d, J=2.4 Hz), 7.37 (2H, d, J=8.1 Hz), 7.67 (1H, s), 7.79 (2H, d, J=8.4 Hz), 7.80 (1H, d, J=9.1 Hz), 10.60 (1H, br s); m/z (ES⁺) 373 (MH⁺). Found: C, 57.66; H,
25 6.12; N, 6.74. C₂₀H₂₄N₂O₃S.HCl.0.4H₂O requires C, 57.72; H, 6.25; N, 6.73%.

EXAMPLE 8

N,N-Dimethyl 2-[1-(4-chlorobenzenesulphonyl)-5-methoxy-1*H*-indol-3-yl]ethylamine Hydrochloride

5 Following a similar procedure to that described in Example 6, but using 4-chlorobenzenesulphonyl chloride instead of benzenesulphonyl chloride, the title compound was prepared in 39% yield as a white solid; mp 222-224°C; δ_{H} (360 MHz, d_6 -DMSO) 2.82 (6H, s), 3.09 (2H, m), 3.35 (2H, m), 3.81 (3H, s), 6.99 (1H, dd, $J=9.0$, 2.5 Hz), 7.27 (1H, d, $J=2.4$ Hz),
10 7.67 (2H, d, $J=8.8$ Hz), 7.70 (1H, s), 7.82 (1H, d, $J=9.0$ Hz), 7.94 (2H, d, $J=8.7$ Hz), 10.65 (1H, br s); m/z (ES⁺) 395/393 (MH⁺). Found: C, 52.76; H, 4.93; N, 6.39. C₁₉H₂₁ClN₂O₃S.HCl.0.2H₂O requires C, 52.71; H, 5.22; N, 6.47%.

EXAMPLE 9

N,N-Dimethyl 2-[1-(3-chlorobenzenesulphonyl)-5-methoxy-1*H*-indol-3-yl]ethylamine Hydrochloride

15 Following a similar procedure to that described in Example 6, but
20 using 3-chlorobenzenesulphonyl chloride instead of benzenesulphonyl chloride, the title compound was prepared in 67% yield as a white solid; mp 191-194°C; δ_{H} (360 MHz, d_6 -DMSO) 2.81 (6H, s), 3.09 (2H, m), 3.34 (2H, m), 3.80 (3H, s), 7.00 (1H, dd, $J=9.0$, 2.5 Hz), 7.26 (1H, d, $J=2.4$ Hz), 7.61 (1H, t, $J=8.0$ Hz), 7.73 (1H, s), 7.77 (1H, dt), 7.84 (1H, d, $J=9.1$ Hz),
25 7.89 (1H, dt), 7.97 (1H, t, $J=1.9$ Hz), 10.59 (1H, br s); m/z (ES⁺) 395/393 (MH⁺). Found: C, 52.88; H, 5.12; N, 6.62. C₁₉H₂₁ClN₂O₃S.HCl requires C, 53.15; H, 5.16; N, 6.52%.

EXAMPLE 10

N,N-Dimethyl 2-[5-methoxy-1-(2-naphthalenesulphonyl)-1*H*-indol-3-yl]ethylamine Hydrochloride

5 Following a similar procedure to that described in Example 6, but using 2-naphthalenesulphonyl chloride instead of benzenesulphonyl chloride, the title compound was prepared in 56% yield as a white solid; mp 191-193°C; δ_{H} (360 MHz, *d*₆-DMSO) 2.81 (6H, s), 3.09 (2H, m), 3.35 (2H, m), 3.78 (3H, s), 6.98 (1H, dd, *J*=9.0, 2.4 Hz), 7.23 (1H, d, *J*=2.4 Hz),
10 7.72 (2H, m), 7.78 (1H, s), 7.81 (1H, dd, *J*=8.8, 1.9 Hz), 7.90 (1H, d, *J*=9.1 Hz), 8.01 (1H, d, *J*=7.7 Hz), 8.08 (1H, d, *J*=8.8 Hz), 8.21 (1H, d), 8.76 (1H, s), 10.60 (1H, br s); *m/z* (ES⁺) 409 (MH⁺). Found: C, 62.19; H, 5.51; N, 6.41. C₂₃H₂₄N₂O₃S.HCl requires C, 62.08; H, 5.66; N, 6.30%.

EXAMPLE 11

N,N-Dimethyl 2-[5-methoxy-1-(4-methoxybenzenesulphonyl)-1*H*-indol-3-yl]ethylamine Hydrochloride

15 Following a similar procedure to that described in Example 6, but
20 using 4-methoxybenzenesulphonyl chloride instead of benzenesulphonyl chloride, the title compound was prepared in 61% yield as a white solid; mp 152-155°C; δ_{H} (360 MHz, *d*₆-DMSO) 2.82 (6H, s), 3.08 (2H, m), 3.34 (2H, m), 3.80 (3H, s), 3.81 (3H, s), 6.98 (1H, dd, *J*=9.0, 2.5 Hz), 7.08 (2H, d, *J*=9.0 Hz), 7.24 (1H, d, *J*=2.4 Hz), 7.67 (1H, s), 7.81 (1H, d, *J*=9.0 Hz), 7.86
25 (2H, d, *J*=9.1 Hz), 10.55 (1H, br s); *m/z* (ES⁺) 389 (MH⁺). Found: C, 56.17; H, 5.94; N, 6.63. C₂₀H₂₄N₂O₄S.HCl requires C, 56.53; H, 5.93; N, 6.59%.

EXAMPLE 12***N,N*-Dimethyl 2-[1-(2-chlorobenzenesulphonyl)-5-methoxy-1*H*-indol-3-yl]ethylamine Hydrochloride**

5 Following a similar procedure to that described in Example 6, but using 2-chlorobenzenesulphonyl chloride instead of benzenesulphonyl chloride, the title compound was prepared in 43% yield as a white solid; mp 185-188°C; δ_{H} (360 MHz, d_6 -DMSO) 2.84 (6H, s), 3.14 (2H, m), 3.37 (2H, m), 3.81 (3H, s), 6.93 (1H, dd, $J=9.0, 2.4$ Hz), 7.31 (1H, d, $J=2.4$ Hz), 10 7.54 (1H, d, $J=9.0$ Hz), 7.63 (1H, td), 7.68 (1H, dd), 7.74 (1H, td), 7.78 (1H, s), 8.14 (1H, dd, $J=7.9, 1.5$ Hz), 10.45 (1H, br s); m/z (ES^+) 395/393 (MH^+). Found: C, 53.09; H, 5.06; N, 6.47. $\text{C}_{19}\text{H}_{21}\text{ClN}_2\text{O}_3\text{S}\cdot\text{HCl}$ requires C, 53.15; H, 5.16; N, 6.52%.

EXAMPLE 13***N,N*-Dimethyl 2-(1-benzoyl-5-methoxy-1*H*-indol-3-yl)ethylamine Hydrogen Oxalate**

15 Following a similar procedure to that described in Example 6, but using benzoyl chloride instead of benzenesulphonyl chloride, the title compound was prepared in 53% yield as a white solid; mp 199-201°C; δ_{H} (360 MHz, d_6 -DMSO) 2.78 (6H, s), 3.05 (2H, m), 3.27 (2H, m), 3.86 (3H, s), 20 7.02 (1H, dd, $J=9.0, 2.4$ Hz), 7.28 (1H, d, $J=2.4$ Hz), 7.32 (1H, s), 7.61 (2H, t, $J=7.0$ Hz), 7.70 (1H, t, $J=7.3$ Hz), 7.75 (2H, d, $J=6.9$ Hz), 8.19 (1H, d, $J=9.0$ Hz); m/z (ES^+) 323 (MH^+). Found: C, 63.89; H, 5.80; N, 7.10. $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_2\cdot\text{C}_2\text{H}_2\text{O}_4$ requires C, 64.07; H, 5.87; N, 6.79%.

EXAMPLE 14*N,N*-Dimethyl 2-[5-methoxy-1-(2-thiophenesulphonyl)-1*H*-indol-3-yl]ethylamine Hydrogen Oxalate

5 Following a similar procedure to that described in Example 6, but using 2-thiophenesulphonyl chloride instead of benzenesulphonyl chloride, the title compound was prepared in 25% yield as a white solid; mp 215-220°C; δ_{H} (360 MHz, *d*₆-DMSO) 2.78 (6H, s), 3.03 (2H, m), 3.29 (2H, m), 3.81 (3H, s), 7.16 (1H, m), 7.20 (1H, d, *J*=2.3 Hz), 7.61 (1H, s), 7.81 (1H, d, *J*=9.2 Hz), 7.83 (1H, m), 8.01 (1H, dd, *J*=5.1, 1.3 Hz); *m/z* (ES⁺) 365 (MH⁺).
10 Found: C, 50.45; H, 4.89; N, 6.27. C₁₇H₂₀N₂O₃S₂.C₂H₂O₄ requires C, 50.21; H, 4.88; N, 6.16%.

EXAMPLE 15

15 2-[1-(Benzenesulphonyl)-5-methoxy-1*H*-indol-3-yl]ethylamine Hydrochloride

 To a stirred solution of 5-methoxytryptamine (3.5 g, 18.4 mmol) in dichloromethane (100 ml) was added dropwise a solution of di-*tert*-butyl
20 dicarbonate (4.02 g, 18.4 mmol) in dichloromethane (25 ml) over 5 minutes. The resulting pale brown solution was allowed to stand at room temperature for 25 h before solvents were removed under vacuum to give a thick oil.

 To a stirred two-phase mixture of a solution of the above 3-[2-(*tert*-
25 butyloxycarbonylamino)ethyl]-5-methoxy-1*H*-indole in dichloromethane (200 ml) and 50% aqueous sodium hydroxide (50 ml) was added tetrabutylammonium hydrogen sulphate (611 mg, 1.8 mmol) and the mixture was stirred for 10 minutes. Benzenesulphonyl chloride (3.52 ml, 27.6 mmol) was added dropwise *via* syringe and the mixture was
30 vigorously stirred for 30 minutes. The mixture was diluted with diethyl ether (500 ml), washed with water (100 ml), brine (2 x 70 ml), dried

(MgSO₄) and concentrated. Flash chromatography of the residue (silica gel, dichloromethane-diethyl ether, 90:10) followed by trituration with hexane-diethyl ether (10:1; 100 ml) afforded 1-(benzenesulphonyl)-3-[2-(*tert*-butyloxycarbonylamino)ethyl]-5-methoxy-1*H*-indole (7.55 g, 95%) as a white solid; δ_{H} (360MHz, CDCl₃) 7.88 (1H, d, J=8.8Hz), 7.84-7.80 (2H, m), 7.54-7.48 (1H, m), 7.45-7.38 (2H, m), 7.32 (1H, s), 6.96-6.90 (2H, m), 4.55 (1H, br s), 3.82 (3H, s), 3.44-3.36 (2H, m), 2.82 (2H, t, J=6.8Hz), 1.45 (9H, s).

A solution of the above protected tryptamine (2.1 g, in a mixture of dichloromethane and trifluoroacetic acid (1:1; 60 ml) was allowed to stand at room temperature for 3 h. The solvents were removed under vacuum and the residue was azeotroped with toluene-methanol (5:1; 100 ml). The residue was dissolved in 4N sodium hydroxide solution (50 ml) and extracted with ethyl acetate (3 x 100 ml). The combined organic solutions were washed with brine (1 x 50 ml), dried (Na₂SO₄) and concentrated. The hydrochloride salt was prepared and recrystallised from acetonitrile to give 1.53 g of the title compound; mp 117-120°C; δ_{H} (360MHz, D₂O) 7.81 (2H, d, J=7.5Hz), 7.74 (1H, d, J=9.0Hz), 7.56 (1H, s), 7.54 (1H, t, J=7.5Hz), 7.41 (2H, t, J=8.1Hz), 7.00 (1H, d, J=2.3Hz), 6.89 (1H, dd, J=9.0 and 2.3Hz), 6.89 (1H, dd, J=9.0 and 2.3Hz), 3.78 (3H, s), 3.29 (2H, t, J=7.6Hz), 3.01 (2H, t, J=7.6Hz); *m/z* (ES) 331 (M⁺+1). (Found: C, 54.07; H, 5.39; N, 7.41. C₁₇H₁₈N₂O₃S.1.0 HCl.0.6 H₂O requires: C, 54.06; H, 5.39; N, 7.42%).

EXAMPLE 16

1-Benzenesulphonyl-5-methoxy-3-[(2-pyrrolidin-1-yl)ethyl]-1*H*-indole
Hydrogen Oxalate

a) Benzenesulphonic acid 2-(1-benzenesulphonyl-5-methoxy-1*H*-indol-3-yl)ethyl ester

To a stirred two-phase mixture of 5-methoxytryptophol (0.150 g, 0.785 mmol) and tetrabutylammonium hydrogen sulphate (27 mg, 0.0785 mmol) in 50% aqueous NaOH (3 ml) and dichloromethane (30 ml) was added benzenesulphonyl chloride (0.25 ml, 1.96 mmol) dropwise over 5 min. The mixture was stirred for 20 min, more benzenesulphonyl chloride (0.10 ml, 0.784 mmol) was added dropwise, and the mixture was stirred for a further hour. The organic layer was washed with brine, dried (Na₂SO₄) and evaporated in vacuo. The residue was purified by flash chromatography (silica gel, 50-100% EtOAc/hexane) to afford 0.095 g (37%) of 2-(1-benzenesulphonyl-5-methoxy-1*H*-indol-3-yl)ethanol and 0.191 g (52%) of the title compound; δ_{H} (360 MHz, *d*₆-DMSO) 2.98 (2H, t, *J* 6.1 Hz), 3.71 (3H, s), 4.30 (2H, t, *J*=6.2 Hz), 6.92 (1H, dd, *J*=8.9, 2.5 Hz), 6.95 (1H, d, *J*=2.2 Hz), 7.47 (2H, t, *J*=7.8 Hz), 7.53-7.59 (3H, m), 7.63-7.67 (4H, m), 7.77 (1H, d, *J*=8.9 Hz), 7.89 (2H, m); *m/z* (ES⁺) 510 (M+K)⁺, 494 (M+Na)⁺, 489 (M+NH₄)⁺, 472 (M+H)⁺.

b) 1-Benzenesulphonyl-5-methoxy-3-[(2-pyrrolidin-1-yl)ethyl]-1*H*-indole Hydrogen Oxalate

To a stirred solution of benzenesulphonic acid 2-(1-benzenesulphonyl-5-methoxy-1*H*-indol-3-yl)ethyl ester (0.191 g, 0.405 mmol) in anhydrous 2-propanol (10 ml) under nitrogen was added anhydrous potassium carbonate (0.112 g, 0.810 mmol), then a solution of pyrrolidine (0.17 ml, 2.03 mmol) in anhydrous 2-propanol (3 ml). The mixture was heated at reflux for 4 h, and the solvents were then removed in vacuo. The residue was partitioned between dichloromethane and water, and the aqueous layer was extracted further with dichloromethane. The combined organic extracts were washed with brine (2 x 25 ml), dried (Na₂SO₄), and evaporated in vacuo. The residue was purified by flash chromatography (silica gel, CH₂Cl₂-MeOH-NH₃; 95:5:0.5) to give 0.102 g

(65%) of the title compound free base. The oxalate salt was prepared in EtOH-Et₂O as a white solid; mp 217-220°C; δ_{H} (360 MHz, *d*₆-DMSO) 1.94 (4H, s), 3.03 (2H, m), 3.27 (4H, s), 3.40 (2H, m), 3.79 (3H, s), 6.98 (1H, dd, J=9.0, 2.3 Hz), 7.17 (1H, d, J=2.3 Hz), 7.58 (2H, t, J=8.0 Hz), 7.69 (2H, m), 7.82 (1H, d, J=9.0 Hz), 7.92 (2H, d, J=7.9 Hz); *m/z* (ES⁺) 385 (MH⁺). Found: C, 57.83; H, 5.31; N, 5.87. C₂₁H₂₄N₂O₃S.C₂H₂O₄ requires C, 58.22; H, 5.52; N, 5.90%.

EXAMPLE 17

1-Benzenesulphonyl-5-methoxy-3-[(2-piperidin-1-yl)ethyl]-1*H*-indole Hydrogen Oxalate

Following a similar procedure to that described in Example 16, step b, but using piperidine instead of pyrrolidine, the title compound was prepared in 90% yield as a white solid; mp 231-234°C; δ_{H} (360 MHz, *d*₆-DMSO) 1.55 (2H, m), 1.75 (4H, m), 3.04 (2H, m), 3.15 (4H, s), 3.27 (2H, m), 3.79 (3H, s), 6.98 (1H, dd, J=9.0, 2.4 Hz), 7.15 (1H, d, J=2.4 Hz), 7.58 (2H, t, J=8.0 Hz), 7.68 (2H, m), 7.82 (1H, d, J=9.0 Hz), 7.91 (2H, d, J=7.7 Hz); *m/z* (ES⁺) 399 (MH⁺). Found: C, 58.40; H, 5.91; N, 5.81. C₂₂H₂₆N₂O₃S.C₂H₂O₄.0.3H₂O requires C, 58.36; H, 5.84; N, 5.67%.

EXAMPLE 18

1-Benzenesulphonyl-5-methoxy-3-[(2-piperazin-1-yl)ethyl]-1*H*-indole Hydrogen Oxalate

Following a similar procedure to that described in Example 16, step b, but using piperazine instead of pyrrolidine, the title compound was prepared in 76% yield as a white solid mp 230-232°C; δ_{H} (360 MHz, *d*₆-DMSO) 2.70 (3H, s), 2.82 (8H, br s), 3.09 (4H, br s), 3.78 (3H, s), 6.96 (1H, dd, J=9.0 Hz), 7.08 (1H, d), 7.57 (2H, t, J=7.5 Hz), 7.60 (1H, s), 7.68 (1H, t, J=7.5 Hz), 7.81 (1H, d, J=9.0 Hz), 7.90 (2H, d, J=7.6 Hz); *m/z* (ES⁺) 414

(MH⁺). Found: C, 44.48; H, 4.85; N, 5.13. C₂₂H₂₇N₃O₃S.4C₂H₂O₄.2H₂O requires C, 44.50; H, 4.86; N, 5.19%.

EXAMPLE 19

5

N,N-Dimethyl 2-(1-benzenesulphonyl-5-methoxy-2-methyl-1*H*-indol-3-yl)ethylamine Hydrogen Oxalate

a) *N,N*-Dimethyl 2-(5-methoxy-2-methyl-1*H*-indol-3-yl)ethylamine

10 To a stirred solution of 2-(5-methoxy-2-methyl-1*H*-indol-3-yl)ethylamine hydrochloride (Spadoni, G. et al. *J. Med. Chem.* **1993**, *36*, 4069-4074) (1.6 g, 6.55 mmol) in methanol (100 ml) was added a 30% w/v solution of sodium methoxide in methanol (1.24 ml, 6.55 mmol), then acetic acid (1.50 ml, 26.2 mmol), followed by sodium cyanoborohydride
15 (0.82 g, 13.1 mmol). A 38% w/v aqueous solution of formaldehyde (1.24 ml, 15.7 mmol) in methanol (30 ml) was then added dropwise over 40 min, and the mixture was stirred overnight before 4N aqueous NaOH (50 ml) was added. The methanol was removed in vacuo and the aqueous residue was extracted with ethyl acetate. The organic extract was washed with brine
20 (50 ml), dried (Na₂SO₄), and evaporated in vacuo to give 1.215 g (80%) of the title compound; δ_{H} (360 MHz, CDCl₃) 2.35 (3H, s), 2.36 (6H, s), 2.50 (2H, m), 3.85 (2H, m), 3.85 (3H, s), 6.76 (1H, dd, *J*=8.7, 2.5 Hz), 6.97 (1H, d, *J*=2.3 Hz), 7.13 (1H, d, *J*=8.5 Hz), 7.72 (1H, br s).

b) *N,N*-Dimethyl 2-(1-benzenesulphonyl-5-methoxy-2-methyl-1*H*-indol-3-yl)ethylamine Hydrogen Oxalate

Following a similar procedure to that described in Example 6, but using *N,N*-dimethyl 2-(5-methoxy-2-methyl-1*H*-indol-3-yl)ethylamine instead of 5-methoxy-*N,N*-dimethyltryptamine the title compound was
30 prepared as a white solid; mp 194-196°C; δ_{H} (360 MHz, *d*₆-DMSO) 2.54 (3H, s), 2.76 (6H, s), 2.98 (2H, m), 3.44 (2H, m), 3.80 (3H, s), 6.92 (1H, dd,

J=9.0, 2.5 Hz), 7.09 (1H, d, J=2.5 Hz), 7.56 (2H, t, J=7.5 Hz), 7.67 (1H, t, J=7.5 Hz), 7.77 (2H, d, J=7.4 Hz), 7.94 (1H, d, J=9.1 Hz); m/z (ES⁺) 373 (MH⁺). Found: C, 56.16; H, 5.52; N, 6.09. C₂₀H₂₄N₂O₃S.C₂H₂O₄.0.4H₂O requires C, 56.25; H, 5.75; N, 5.96%.

5

Examples 20, 21 and 22 were prepared from the appropriate tryptamine compounds and the corresponding sulphonyl chloride following similar methods to that described for Example 6.

10

EXAMPLE 20

N,N-Dimethyl 2-(1-Benzenesulphonyl-1H-indol-3-yl)ethylamine Hydrogen Oxalate

mp 196-198°C (EtOH-Et₂O); δ_H (360MHz, DMSO-d₆) 7.97-7.91 (3H, m), 7.74 (1H, s), 7.72-7.64 (2H, m), 7.61 (2H, t, J=8.0Hz), 7.38 (1H, t, J=7.3Hz), 7.29 (1H, t, J=7.3Hz), 3.34-3.26 (2H, m), 7.08-3.00 (2H, m), 2.77 (6H, s); m/z (CI) 329 (M⁺+1). (Found: C, 57.06; 5.40, N, 6.58. C₁₈H₂₀N₂O₂S.1.0 C₂H₂O₄ requires: C, 57.40; H, 5.30; N, 6.69%).

20

EXAMPLE 21

N,N-Dimethyl 2-(1-methylsulphonyl-1H-indol-3-yl)ethylamine. Hydrogen Oxalate

mp 191-193°C (EtOH-Et₂O); δ_H (360MHz, DMSO-d₆) 7.83 (1H, d, J=8.1Hz), 7.75 (1H, d, J=7.3Hz), 7.52 (1H, s), 7.44-7.30 (2H, m), 3.37 (3H, s), 3.36-3.28 (2H, m), 3.14-3.05 (2H, m), 2.79 (6H, s); m/z (CI) 267 (M⁺+1). (Found: C, 49.93; H, 5.52; N, 7.76. C₁₃H₁₈N₂O₂S.1.1 C₂H₂O₄ requires: C, 49.96; H, 5.57; N, 7.67%).

EXAMPLE 22

N,N-Dimethyl 2-(5-methoxy-1-methylsulphonyl-1*H*-indol-3-yl)ethylamine.

Hydrogen Oxalate

5 mp 201-203°C (EtOH-Et₂O); δ_{H} (360MHz, DMSO-d₆) 7.71 (1H, d, J=9.0Hz), 7.48 (1H, s), 7.25 (1H, d, J=2.4Hz), 7.01 (1H, dd, J=9.0 and 2.4Hz), 3.83 (3H, s), 3.36-3.28 (5H, m and s), 3.10-3.02 (2H, m), 2.79 (6H, s); m/z (CI) 297 (M⁺+1). (Found: C, 49.74; H, 5.56; N, 7.07. C₁₄H₂₀N₂O₃S.1.0 C₂H₂O₄ requires: C, 49.73; H, 5.74; N, 7.25%).

10

EXAMPLE 23

[3-(2-Dimethylamino-ethyl)-5-hydroxy-1*H*-indol-1-yl]phenylmethanone

15 a) 2-(5-Benzoyloxy-1*H*-indol-3-yl)-*N,N*-dimethyl-2-oxo-acetamide

Oxalyl chloride (3.9 ml, 45 mmol) was added to a stirred solution of 5-benzyloxyindole (5.0g, 22 mmol) in dry tetrahydrofuran (200 ml), at 0°C under nitrogen. The cooling bath was removed and the reaction was stirred at room temperature for 3 hours. The reaction was then cooled to 20 0°C and dimethylamine was bubbled through the solution for 5 minutes (a heavy white precipitate forms). The whole mixture was then poured into 4N hydrochloric acid (50 ml). The layers were separated and the aqueous was extracted with diethylether (x1). The combined organic layers were dried (Na₂SO₄), filtered and evaporated to give the title compound (6.4g, 25 89%) as an off-white solid; δ_{H} (360 MHz, *d*₆-DMSO) 2.90 (3H, s), 2.98 (3H, s), 5.14 (2H, s), 6.99 (1H, dd, J = 8.3 and 2.0 Hz), 7.31-7.50 (6H, m), 7.71 (1H, d, J = 2.0 Hz), 8.02 (1H, s), 12.2 (1H, br s).

b) [2-(5-Benzoyloxy-1*H*-indol-3-yl)ethyl]dimethylamine

30 A solution of lithium aluminium hydride (1.0M, 120 ml, 120 mmol) was added to a stirred solution of 2-(5-benzyloxy-1*H*-indol-3-yl)-*N,N*-

dimethyl-2-oxo-acetamide (6.4g, 19.9 mmol) in dry tetrahydrofuran (100 ml) at room temperature under nitrogen. (Gas evolution and precipitate formation were observed) The reaction was then stirred and heated at reflux for 4 hours. The mixture was then cooled to 0°C, and quenched with water (4.5 ml), 4N sodium hydroxide (4.5 ml). Ethyl acetate and anhydrous sodium sulphate were then added. After stirring at room temperature overnight, the precipitate was removed by filtration (washing with ethyl acetate). The filtrate was evaporated and the residue was purified by chromatography on silica gel, eluting with dichloromethane/methanol/aqueous ammonia (80:8:1) to give the title amine (4.0g, 68%) as a thick oil which solidifies upon standing; δ_{H} (360 MHz, CDCl_3) 2.33 (6H, s), 2.58-2.62 (2H, m), 2.87-2.91 (2H, m), 5.10 (2H, s), 6.92 (1H, dd, $J=8.8$ and 2.4 Hz), 6.98 (1H, d, $J=2.2$ Hz), 7.12 (1H, d, $J=2.4$ Hz), 7.23-7.48 (6H, m), 8.0 (1H, br s).

c) [5-Benzyloxy-3-(2-dimethylamino-ethyl)-1*H*-indol-1-yl]phenylmethanone

Benzoyl chloride (217 ml, 1.9 mmol) was added to a stirred solution of [2-(5-benzyloxy-1*H*-indol-3-yl)ethyl]dimethylamine (500 mg, 1.7 mmol), triethylamine (473 ml, 3.4 mmol) and 4-(dimethylamino)pyridine (20 mg, 0.2 mmol) in dry dichloromethane (5 ml) at 0°C. The reaction was allowed to warm slowly to ambient temperature, and stirred at this temperature overnight. The reaction was quenched with saturated aqueous sodium hydrogen carbonate. The aqueous was then extracted with dichloromethane (x3). The combined extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified by chromatography on silica gel, eluting with dichloromethane/methanol/aqueous ammonia (80:8:1) to give the title compound (327 mg, 48%) as a thick oil. δ_{H} (250 MHz, CDCl_3) 2.30 (6H, s), 2.52-2.60 (2H, m), 2.78-2.84 (2H, m), 5.16 (2H, s), 7.06-7.10 (3H, m), 7.30-7.64 (10H, m), 8.28 (0.5H, s), 8.32 (0.5H, s).

d) [3-(2-Dimethylamino-ethyl)-5-hydroxy-1*H*-indol-1-yl]phenylmethanone

A solution of [5-benzyloxy-3-(2-dimethylamino-ethyl)-1*H*-indol-1-yl]phenylmethanone (300 mg, 0.75 mmol) and 4N hydrochloric acid (190 ml, 0.76 mmol) in ethanol (10 ml) was hydrogenated over 10% palladium on carbon (100 mg) at 35 psi for 3 hours. The catalyst was removed by filtration. The filtrate was evaporated, and the residue was partitioned between dichloromethane and saturated aqueous sodium hydrogen carbonate. The aqueous was further extracted with dichloromethane (x2). The combined extracts were dried (K₂CO₃), filtered and evaporated. The residue was purified by chromatography on silica gel, eluting with dichloromethane /methanol/aqueous ammonia (80:8:1) to give the title compound (120 mg, 52%), as a colourless solid; mp 154-156°C. δ_H (360 MHz, CDCl₃) 2.40 (6H, s), 2.70-2.75 (2H, m), 2.83-2.88 (2H, m), 6.86-6.90 (2H, m), 7.04 (1H, s), 7.49-7.61 (3H, m), 7.68-7.71 (2H, m), 8.17 (0.5H, s), 8.20 (0.5H, s). m/z (CI⁺) 309 [MH]⁺. Found: C, 73.22; H, 6.48; N, 8.74. C₁₉H₂₀N₂O₂ · 0.2 H₂O requires C, 73.15; H, 6.59; N, 8.98%.

EXAMPLE 2420 3-(2-Dimethylamino-ethyl)-5-hydroxy-1*H*-indole-1-carboxylic acid *tert*-butyl estera) 5-Benzyloxy-3-(2-dimethylamino-ethyl)-1*H*-indole-1-carboxylic acid *tert*-butyl ester

25 Di-*tert*-butyl dicarbonate (408 mg, 1.9 mmol) was added to a stirred solution of [2-(5-benzyloxy-1*H*-indol-3-yl)ethyl]dimethylamine (500 mg, 1.7 mmol), triethylamine (473 ml, 3.4 mmol) and 4-(dimethylamino)-pyridine (20 mg, 0.2 mmol) in dry dichloromethane (5 ml) at 0°C. The reaction was allowed to warm slowly to ambient temperature. After 3 hours the mixture was poured into saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane (x3). The combined extracts were

dried (Na_2SO_4), filtered and evaporated. The residue was purified by chromatography on silica gel, eluting with dichloromethane/methanol/aqueous ammonia (80:8:1) to give the title compound (630 mg, 95%) as a thick oil. δ_{H} (360 MHz, CDCl_3) 1.65 (9H, s), 2.33 (6H, s), 2.58-2.62 (2H, m), 2.79-2.83 (2H, m), 5.12 (2H, s), 6.99 (1H, dd, $J=9.0$ and 2.5 Hz), 7.06 (1H, d, $J=2.5$ Hz), 7.29-7.48 (6H, m), 8.0 (1H, br d).

b) 3-(2-Dimethylamino-ethyl)-5-hydroxy-1H-indole-1-carboxylic acid tert-butyl ester

A solution of 5-benzyloxy-3-(2-dimethylamino-ethyl)-1H-indole-1-carboxylic acid tert-butyl ester (303 mg, 0.77 mmol) and 4N hydrochloric acid (192 ml, 0.77 mmol) in ethanol (10 ml) was hydrogenated over 10% palladium on carbon (100 mg) at 40 psi for 4 hours. The catalyst was removed by filtration. The filtrate was evaporated and the residue was partitioned between aqueous sodium hydrogen carbonate and dichloromethane. The aqueous was further extracted with dichloromethane (x2). The combined extracts were dried (K_2CO_3), filtered and evaporated. The residue was purified by chromatography on silica gel, eluting with dichloromethane/methanol/aqueous ammonia (60:8:1) to give the title compound (117 mg, 50%) as a colourless solid. δ_{H} (360 MHz, CDCl_3) 1.64 (9H, s), 2.45 (6H, s), 2.73 -2.80 (2H, m), 2.88-2.93 (2H, m), 6.82-6.85 (1H, m), 6.96 (1H, br s), 7.33 (1H, br s), 7.92 (1H, m). m/z (CI^+) 305 $[\text{MH}]^+$. Found: C, 64.07; H, 8.07; N, 8.71. $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_3 \cdot 0.8 \text{H}_2\text{O}$ requires C, 64.01; H, 8.15; N, 8.78%.

EXAMPLE 25***N,N*-Dimethyl 2-(1-Benzenesulphonyl-5-benzyloxy-1*H*-indol-3-yl)ethylamine Hydrogen Oxalate**

5 To a stirred solution of 5-benzyloxytryptamine hydrochloride (2.29 g, 7.56 mmol) in methanol (100 ml) was added sodium methoxide (30% w/v in methanol; 1.44 ml) followed by glacial acetic acid (1.70 ml, 30.2 mmol) and sodium cyanoborohydride (950 mg, 15.12 mmol). A solution of formaldehyde (38% w/v aqueous solution; 1.43 ml) in methanol (25 ml) was
10 then added dropwise over 20 minutes, and the resulting solution was stirred at room temperature for 4 h. 4N Sodium hydroxide (60 ml) was added and the methanol was removed under vacuum. The aqueous residue was extracted with diethyl ether (2 x 250 ml) and the combined organic phases were washed with brine (2 x 50 ml), dried (Na₂SO₄) and
15 concentrated. The residue was dissolved in dichloromethane (120 ml) and 50% aqueous sodium hydroxide (40 ml) was added followed by tetrabutylammonium hydrogen sulphate (258 mg). The mixture was vigorously stirred, benzenesulphonyl chloride (1.45 ml) in dichloromethane (10 ml) was added dropwise over 3 minutes and stirring was continued for
20 30 minutes. Water (120 ml) and diethyl ether (200 ml) were added and the organic phase was decanted off, washed with brine (2 x 50 ml), dried (Na₂SO₄) and concentrated. Flash chromatography of the residue (silica gel, dichloromethane-methanol-ammonia, 95:5:0.5) afforded 2.57 g (78%) of the title compound free base as a colourless thick oil. The oxalate salt
25 was prepared; mp 212-215°C (EtOH); δ_H (360MHz, DMSO-d₆) 7.94-7.90 (2H, m), 7.82 (1H, d, J=9.0Hz), 7.72-7.64 (2H, m), 7.58 (2H, t, J=8.0Hz), 7.48-7.28 (6H, m), 7.06 (1H, dd, J=9.0 and 2.4Hz), 5.12 (2H, s), 3.30-3.22 (2H, m), 3.06-2.98 (2H, m), 2.77 (6H, s); m/z (ES) 435 (M⁺+1). (Found: C, 61.81; H, 5.38; N, 5.48. C₂₅H₂₆N₂O₃S.1.0 C₂H₂O₄ requires: C, 61.82; H, 5.38; N, 5.34%).
30

EXAMPLE 26

N,N-Dimethyl 2-(1-benzenesulphonyl-5-hydroxy-1*H*-indol-3-yl)ethylamine

A solution of *N,N*-dimethyl 2-(1-benzenesulphonyl-5-benzyloxy-1*H*-indol-3-yl)ethylamine (2.25 g, 4.6 mmol) in absolute ethanol (100 ml) was hydrogenated at 40 psi over 20% palladium hydroxide (600 mg) for 4.5 h. Additional catalyst (1.6 g) was then added and hydrogenation was resumed at 45 psi for 2.5h. The catalyst was removed by filtration, washed with a mixture of dichloromethane-methanol-ammonia (80:20:2; 3 x 70 ml), and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography (silica gel, dichloromethane-methanol-ammonia, 95:5:0.5) to give the title compound as a crystalline solid after trituration with diethyl ether (30 ml); mp 185-188°C; δ_H (360MHz, DMSO- d_6) 9.32 (1H, br s), 7.90-7.84 (2H, m), 7.69 (1H, d, J=8.7Hz), 7.68-7.62 (1H, m), 7.55 (2H, t, J=8.0Hz), 7.48 (1H, s), 6.82 (1H, d, J=2.2Hz), 6.78 (1H, dd, H=8.8 and 2.2 Hz), 2.67 (2H, t, J=7.6Hz), 2.47 (2H, t, J=7.6Hz), 2.18 (6H, s); m/z (ES) 345 (M^++1). (Found: C, 62.91; H, 5.86; N, 8.16. $C_{18}H_{20}N_2O_3$ requires: C, 62.77; H, 5.85; N, 8.13%).

EXAMPLE 27

N,N-Dimethyl 2-(1-benzenesulphonyl-5-cyano-1*H*-indol-3-yl)ethylamine Hydrogen Oxalate

To a stirred solution of 3-(2-aminoethyl)-5-cyano-1*H*-indole hydrochloride (Castro, J. L. et al. *J. Med. Chem.* **1994**, *37*, 3023-3032) (0.1208 g, 0.545 mmol) in methanol (25 ml) was added a 30% w/v solution of sodium methoxide in methanol (0.1 ml, 0.545 mmol), then acetic acid (0.125 ml, 2.18 mmol), followed by sodium cyanoborohydride (68 mg, 1.09 mmol). A 38% w/v aqueous solution of formaldehyde (0.103 ml, 1.31 mmol) in methanol (10 ml) was then added dropwise over 30 min. The mixture was stirred for 3.5 h, then 4N aqueous NaOH (25 ml) was added, and the

methanol was removed in vacuo. The aqueous residue was extracted with diethyl ether (3 x 25 ml), and the combined organic extracts were washed with brine (2 x 20 ml), dried (Na₂SO₄), and evaporated in vacuo to give crude *N,N*-dimethyl 2-(5-cyano-1*H*-indol-3-yl)ethylamine.

To this crude product was added dichloromethane (30 ml), 50% aqueous NaOH (2 ml), and tetrabutylammonium hydrogen sulphate (19 mg, 0.0545 mmol). Benzenesulphonyl chloride (0.104 ml, 0.817 mmol) was then added dropwise over 3 min whilst stirring magnetically, and the mixture was stirred for 30 min. Ethyl acetate (50 ml) and water (25 ml) was then added, and the organic layer was washed with brine (2 x 25 ml), dried (Na₂SO₄), and evaporated in vacuo. The residue was purified by flash chromatography (silica gel, CH₂Cl₂-MeOH-NH₃(aq); 95:5:0.5) to yield 0.132 g (66%) of the title compound free base. The oxalate salt was prepared in EtOH-Et₂O as a white solid; mp 213-220°C; δ_H (360 MHz, *d*₆-DMSO) 2.78 (6H, s), 3.10 (2H, m), 3.31 (2H, m), 7.63 (2H, t, J=7.5 Hz), 7.74 (1H, t, J=7.5 Hz), 7.78 (1H, dd, J=8.6, 1.4 Hz), 7.98 (1H, s), 8.03 (2H, d, J=7.4 Hz), 8.11 (1H, d, J=8.4 Hz), 8.31 (1H, s); *m/z* (ES⁺) 354 (MH⁺). Found: C, 57.01; H, 4.83; N, 9.22. C₁₉H₁₉N₃O₂S.C₂H₂O₄ requires C, 56.88; H, 4.77; N, 9.48%.

EXAMPLE 28

N,N-Dimethyl 2-(1-benzenesulphonyl-5-methoxy-2,3-dihydro-1*H*-indol-3-yl)ethylamine Hydrogen Oxalate

a) *N,N*-Dimethyl 2-(5-methoxy-2,3-dihydro-1*H*-indol-3-yl)ethylamine

A mixture of 5-methoxy-*N,N*-dimethyltryptamine (0.200g, 0.939 mmol) and palladium on carbon (10%, 200 mg) in 5 M aqueous HCl (50 ml) was hydrogenated at 50 psi overnight. The catalyst was removed by filtration, and the filtrate was extracted with dichloromethane (3 x 25 ml). The combined organic extracts were evaporated in vacuo and the residue

was purified by flash chromatography (silica gel, CH₂Cl₂-MeOH-NH₃(aq); 92:8:0.8) to give 94 mg (47%) of the title compound; δ_{H} (250 MHz, CDCl₃) 1.71 (1H, m), 1.99 (1H, m), 2.26 (6H, s), 2.37 (2H, m), 3.20 (1H, t, J=8.0 Hz), 3.27 (1H, m), 3.68 (1H, t, J=8.0 Hz), 3.75 (3H, s), 6.60-6.61 (2H, m), 6.73 (1H, m).

b) *N,N*-Dimethyl 2-(1-benzenesulphonyl-5-methoxy-2,3-dihydro-1*H*-indol-3-yl)ethylamine Hydrogen Oxalate

Following a similar procedure to that described in Example 6, but using *N,N*-dimethyl 2-(5-methoxy-2,3-dihydro-1*H*-indol-3-yl)ethylamine instead of 5-methoxy-*N,N*-dimethyltryptamine, the title compound was prepared in 57% yield as a white solid; mp 183-185°C; δ_{H} (360 MHz, *d*₆-DMSO) 1.47 (1H, m); 1.94 (1H, m), 2.68 (6H, s), 2.96 (2H, m), 3.14 (1H, m), 3.63 (1H, m), 3.71 (3H, s), 4.06 (1H, m), 6.82 (2H, m), 7.42 (1H, d, J=9.4 Hz), 7.57 (2H, t, J=7.3 Hz), 7.68 (1H, t), 7.78 (2H, d, J=7.6 Hz); *m/z* (ES⁺) 361 (MH⁺). Found: C, 54.29; H, 5.56; N, 5.97. C₁₉H₂₄N₂O₃S.C₂H₂O₄.0.7H₂O requires C, 54.46; H, 5.96; N, 6.05%.

EXAMPLE 29

trans-4-Dimethylamino-1-(4-methylbenzenesulphonyl)-1,3,4,5-tetrahydro-benz[*cd*]indol-5-ol. Hydrogen Oxalate

A suspension of (±)-4-azido-3,4-dihydro-1-[(methylphenyl)sulphonyl]benz[*cd*]indol-5(1H)one (*J. Chem. Soc. Perkin Trans. I*, **1973**, 438-442) (11.9 g) in absolute ethanol (400 ml) and concentrated hydrochloric acid (11.9 ml) was hydrogenated at 25 psi over 10% palladium on carbon (1.2 g) for 6 h. The mixture was diluted with absolute ethanol (300 ml), 10% palladium on carbon (2 g) was added and hydrogenation was resumed for another 16 h at 25 psi. The catalyst was removed by filtration, washed with absolute ethanol (3 x 125 ml) and the filtrate was concentrated under vacuum. The residue was crystallised

from ethanol to give 4.55 g of (\pm)-4-amino-3,4-dihydro-1-[(methylphenyl)sulphonylbenz[cd]indol-5(1H)one hydrochloride as a white solid.

To a solution of sodium borohydride (1 g) in absolute ethanol (75 ml) was added dropwise *via* cannula a suspension of the above aminoketone hydrochloride (4.55 g) in absolute ethanol (150 ml) over 15 minutes, keeping the internal temperature below 3°C. The resulting mixture was stirred at -2°C for 1h 40 min under nitrogen before it was carefully acidified with 2N hydrochloric acid (28 ml). The ethanol was removed under vacuum and the residue was basified with 2N sodium hydroxide (35 ml). The products were extracted with ethyl acetate (3 x 150 ml) and the combined organic phases were washed with brine (50 ml), dried (Na₂SO₄) and concentrated. Flash chromatography of the residue (silica gel, dichloromethane-ethanol-ammonia, 170:28:3) gave 3.99 g (97%) of 4-amino-1-(4-methyl)benzenesulphonyl-1,3,4,5-tetrahydrobenz[cd]indol-5-ol as a 90:10 mixture of trans and cis isomers; *m/z* 342 (M⁺).

A solution of the above aminoalcohol (3.97 g, 11.59 mmol) in absolute ethanol (150 ml), aqueous formaldehyde (38% w/v; 9.2 ml) and glacial acetic acid (92 ml) was hydrogenated at 30 psi over 10% palladium on carbon (1.56 g) for 65 h. The catalyst was filtered off, washed with absolute ethanol and the filtrate was concentrated under vacuum. The residue was dissolved in dichloromethane (40 ml) and washed with 10% aqueous sodium hydrogen carbonate (100 ml). The aqueous layer was extracted with dichloromethane (2 x 120 ml) and the combined organic phases were dried (Na₂SO₄) and concentrated. Flash chromatography of the residue (silica gel, dichloromethane-ethanol-ammonia, 85:15:0 to 1750:225:25) gave 3.68 g (86%) of the title compound free base together with 400 mg of the corresponding *cis*-isomer. The oxalate salt was prepared from ethanol-diethyl ether; mp 123-126°C; δ_H (360MHz, DMSO-d₆) 7.86 (2H, d, J=8.4Hz), 7.76 (1H, d, J=8.1Hz), 7.55 (1H, s), 7.44-7.36 (3H, m), 7.30 (1H, d, J=7.4Hz), 5.14 (1H, d, J=9.3Hz), 3.54-3.38 (1H, m),

3.26-3.16 (1H, m), 3.12-2.96 (1H, m), 2.78 (6H, s), 2.32 (3H, s); m/z (EI) 371 ($M^{+}+1$). (Found: C, 57.16; H, 5.36; N, 5.99. $C_{20}H_{22}N_2O_3S \cdot 1.0 C_2H_2O_4$ requires: C, 57.38; H, 5.25; N, 6.08%). [*J Chem Soc. Perkin Trans I*, **1973**, 438-442]

5

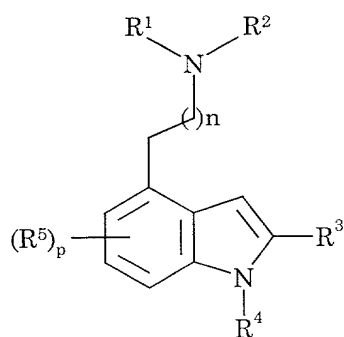
EXAMPLE 30

4-Dimethylamino-5-methoxy-1-(4-methylbenzenesulphonyl)-1,3,4,5-tetrahydro-benz[cd]indole Hydrogen Oxalate

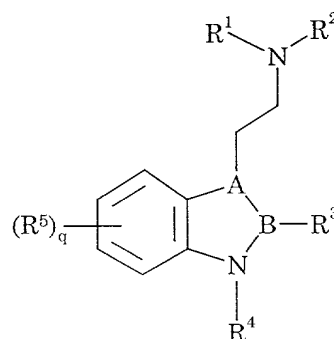
10 To a solution of the product from Example 29 (free base; 700 mg) in anhydrous tetrahydrofuran (10 ml) and anhydrous dimethylformamide (3 ml) was added sodium hydride (60% dispersion in oil; 91 mg) followed, after 10 minutes, by benzyltrimethylammonium chloride (35 mg) and methyl 3-bromopropionate. After stirring at room temperature for 2.5 h,
15 additional sodium hydride was added and stirring was continued for 16 h. Water (50 ml) was added and products were extracted with dichloromethane (3 x 50 ml), then dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (silica gel, dichloromethane-ethanol, 95:5) gave 30 mg of the title compound free base. The oxalate salt was prepared
20 and crystallised from isopropanol; mp 133-136°C; δ_H (360MHz, DMSO- d_6) 7.86 (2H, d, $J=8.4Hz$), 7.80 (1H, d, $J=8.1Hz$), 7.52 (1H, s), 7.42-7.34 (3H, m), 7.29 (1H, d, $J=7.3Hz$), 4.89 (1H, d, $J=6.5Hz$), 3.56-3.48 (4H, m and s), 3.08 (2H, d, $J=5.6Hz$), 2.52 (6H, s), 2.31 (3H, s); m/z 384 (M^{+}). (Found: C, 58.01; H, 5.84; N, 5.77. $C_{21}H_{24}N_2O_3S \cdot 1.0 C_2H_2O_4$ requires: C, 58.22; H,
25 5.52; N, 5.90%).

WHAT IS CLAIMED IS:

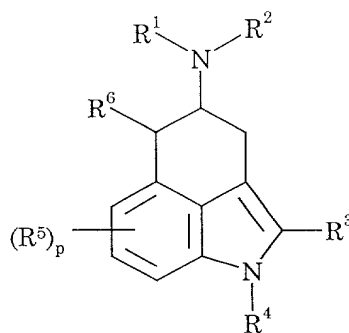
1. A method for the treatment and/or prevention of a clinical condition for which selective agonism or antagonism of 5-HT₆ receptors is indicated comprising administering to a patient in need of such treatment an effective amount of a compound, or a pharmaceutically acceptable salt or prodrug thereof, having a structure in accordance with Formula I, II or III:



(I)



(II)



(III)

wherein

n is 1 or 2;

p is 0,1,2 or 3;

q is 0,1,2,3 or 4;

R¹ and R² independently represent hydrogen, C₁₋₆ alkyl or aryl (C₁₋₆)alkyl, or together represent the atoms necessary to complete a heterocycloalkyl group comprising the nitrogen atom to which R¹ and R² are attached;

5 R³ represents hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl(C₁₋₆)alkyl, aryl, heteroaryl, arylcarbonyl, heteroarylcarbonyl or C₁₋₆ alkylcarbonyl;

R⁴ represents arylsulphonyl, heteroarylsulphonyl, C₁₋₆ alkylsulphonyl, di(C₁₋₆)alkylaminosulphonyl, arylcarbonyl, C₁₋₆ alkylcarbonyl, heteroarylcarbonyl or C₁₋₆ alkoxycarbonyl;

10 each R⁵ independently represents hydroxy, C₁₋₆ alkoxy, aryl(C₁₋₆)alkoxy, nitrile or halogen;

R⁶ represents hydrogen, hydroxy or C₁₋₆ alkoxy; and

-A-B- represents -C=C- or -CH-CH-.

15

2. The method of claim 1 in which said compound is in accordance with said Formula I, II or III wherein:

R¹ and R² independently represent hydrogen, methyl, ethyl, propyl or benzyl, or R¹ and R² in combination represent pyrrolidinyl, piperidinyl, 20 piperazinyl, 4-methylpiperazinyl or morpholinyl;

R³ represents hydrogen, methyl, ethyl, benzyl, allyl, propargyl, benzoyl, phenyl, thienyl or furoyl;

R⁴ represents benzenesulphonyl, naphthalene-2-sulphonyl, o-, m- or p-toluenesulphonyl, o-, m- or p-chlorobenzenesulphonyl, o-, m- or p-methoxybenzenesulphonyl, methanesulphonyl, dimethylaminosulphonyl, 25 thienylsulphonyl, benzoyl, acetyl, furoyl or *tert*-butoxycarbonyl; and

R⁵ represents hydroxy, methoxy, ethoxy, propoxy, benzyloxy, nitrile, fluorine, chlorine or bromine.

30

3. The method of claim 1 or claim 2 in which the compound is selected from:

(a) compounds of Formula I in which p is zero; R¹ and R² are identical and represent hydrogen or methyl; R³ represents hydrogen or benzoyl; and R⁴ represents arylsulphonyl or dimethylaminosulphonyl;

(b) compounds of Formula II in which R¹ and R² are identical and represent hydrogen or methyl, or together complete a pyrrolidinyl, piperidinyl, piperazinyl or 4-methylpiperazinyl ring; R³ represents hydrogen or methyl; R⁴ represents arylsulphonyl, thienylsulphonyl, benzoyl or *tert*-butoxycarbonyl; R⁵ represents hydroxy, methoxy, benzyloxy or nitrile; and q is zero or 1; and

(c) compounds of Formula III in which R¹ and R² are identical and represent hydrogen or methyl; R³ represents hydrogen; R⁴ represents arylsulphonyl; R⁶ represents hydroxy or methoxy; and p is zero.

4. The method according to claim 1 in which the compound is selected from:

2-[1-(benzenesulphonyl)-1*H*-indol-4-yl]ethylamine;

N,N-dimethyl 2-[1-(benzenesulphonyl)-1*H*-indol-4-yl]ethylamine;

N,N-dimethyl 2-[1-(dimethylamino)sulphonyl-1*H*-indol-4-yl]ethylamine;

N,N-dimethyl 3-[1-(benzenesulphonyl)-1*H*-indol-4-yl]propylamine;

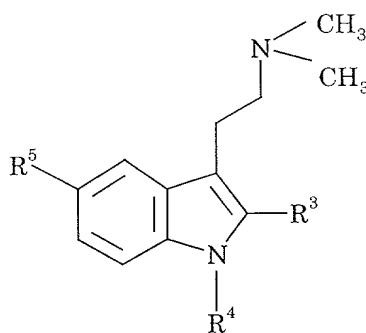
N,N-dimethyl 2-[1-(benzenesulphonyl)-2-benzoyl-1*H*-indol-4-yl]ethylamine;

trans-4-dimethylamino-1-(4-methylbenzenesulphonyl)-1,3,4,5-tetrahydro-benz[*cd*]indol-5-ol; and

4-dimethylamino-5-methoxy-1-(4-methylbenzenesulphonyl)-1,3,4,5-tetrahydro-benz[*cd*]indole;

or pharmaceutically acceptable salts or prodrugs thereof.

5. The method of claim 1 in which the compound is in accordance with Formula II(a):



(II(a))

where R³, R⁴ and R⁵ are as defined in claim 1.

6. The method of claim 5 in which said compound is selected from:

N,N-dimethyl 2-[1-(benzenesulphonyl)-5-methoxy-1*H*-indol-3-yl]ethylamine;

N,N-dimethyl 2-[5-methoxy-1-(4-methylbenzenesulphonyl)-1*H*-indol-3-yl]ethylamine;

N,N-dimethyl 2-[1-(4-chlorobenzenesulphonyl)-5-methoxy-1*H*-indol-3-yl]ethylamine;

N,N-dimethyl 2-[1-(3-chlorobenzenesulphonyl)-5-methoxy-1*H*-indol-3-yl]ethylamine;

N,N-dimethyl 2-[5-methoxy-1-(2-naphthalenesulphonyl)-1*H*-indol-3-yl]ethylamine;

N,N-dimethyl 2-[5-methoxy-1-(4-methoxybenzenesulphonyl)-1*H*-indol-3-yl]ethylamine;

N,N-dimethyl 2-[1-(2-chlorobenzenesulphonyl)-5-methoxy-1*H*-indol-3-yl]ethylamine;

N,N-dimethyl 2-(1-benzoyl-5-methoxy-1*H*-indol-3-yl)ethylamine;

N,N-dimethyl 2-[5-methoxy-1-(2-thiophenesulphonyl)-1*H*-indol-3-yl]ethylamine;

N,N-dimethyl 2-(1-benzenesulphonyl-5-methoxy-2-methyl-1*H*-indol-3-yl)ethylamine;

N,N-dimethyl 2-(1-benzenesulphonyl-1*H*-indol-3-yl)ethylamine;

N,N-dimethyl 2-(1-methylsulphonyl-1*H*-indol-3-yl)ethylamine;

5 *N,N*-dimethyl 2-(5-methoxy-1-methylsulphonyl-1*H*-indol-3-yl)ethylamine;

[3-(2-dimethylamino-ethyl)-5-hydroxy-1*H*-indol-1-yl]phenylmethanone;

3-(2-dimethylamino-ethyl)-5-hydroxy-1*H*-indole-1-carboxylic acid *tert*-butyl ester;

N,N-dimethyl 2-(1-benzenesulphonyl-5-benzyloxy-1*H*-indol-3-

10 yl)ethylamine;

N,N-dimethyl 2-(1-benzenesulphonyl-5-hydroxy-1*H*-indol-3-yl)ethylamine;

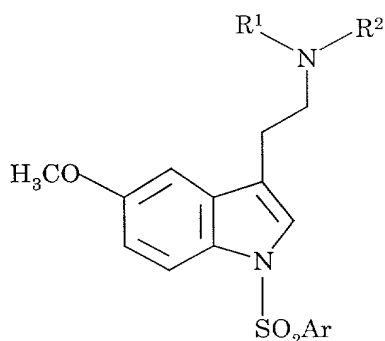
and

N,N-dimethyl 2-(1-benzenesulphonyl-5-cyano-1*H*-indol-3-yl)ethylamine;

and pharmaceutically acceptable salts or prodrugs thereof.

15

7. The method of claim 1 in which the compound is in accordance with Formula II(b):



(II(b))

20

where R¹ and R² are as defined in claim 1, and Ar represents an aryl group.

8. The method of claim 7 in which said compound is selected from:

2-[1-(benzenesulphonyl)-5-methoxy-1*H*-indol-3-yl]ethylamine;

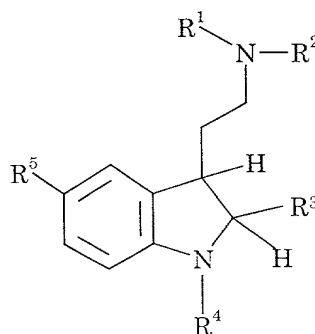
1-benzenesulphonyl-5-methoxy-3-[(2-pyrrolidin-1-yl)ethyl]-1*H*-indole;

5 1-benzenesulphonyl-5-methoxy-3-[(2-piperidin-1-yl)ethyl]-1*H*-indole; and

1-benzenesulphonyl-5-methoxy-3-[(2-piperazin-1-yl)ethyl]-1*H*-indole

and pharmaceutically acceptable salts or prodrugs thereof.

9. The method of claim 1 in which the compound is in
10 accordance with Formula II(c):



(II(c))

where R¹ - R⁵ are as defined in claim 1.

10. The method of claim 9 in which said compound is:

15 *N,N*-dimethyl 2-(1-benzenesulphonyl-5-methoxy-2,3-dihydro-1*H*-indol-3-yl)ethylamine;

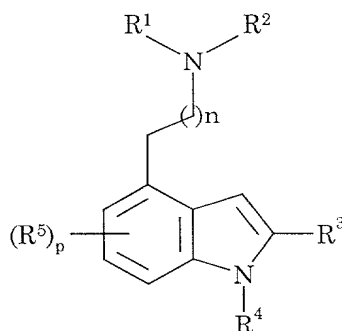
or a pharmaceutically acceptable salt or prodrug thereof.

11. The method of claim 1 in which the compound has a 5-HT₆
20 receptor (rat or human) binding affinity (K_i), when measured in cell lines expressing cloned recombinant 5-HT₆ receptors, of less than 1μM, and has a selective affinity for 5-HT₆ receptors relative to 5-HT₅ and/or 5-HT₇ receptors of at least 3-fold.

12. The method of claim 1 in which the clinical condition is selected from the group consisting of:

Parkinson's disease, Huntington's disease, anxiety, depression, manic depression, psychosis, epilepsy, obsessive compulsive disorders, migraine, Alzheimers disease, sleep disorders, feeding disorders including anorexia and bulimia, panic attacks, withdrawal from drug abuse including abuse of cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, disorders associated with spinal trauma and/or head injury hydrocephalus, and GI (gastrointestinal) disorders including IBS (Irritable Bowel Syndrome).

13. A compound of Formula I:



(I)

wherein

n is 1 or 2;

p is 0, 1, 2 or 3;

R^1 and R^2 independently represent hydrogen, C_{1-6} alkyl or aryl (C_{1-6})alkyl, or together represent the atoms necessary to complete a heterocycloalkyl group comprising the nitrogen atom to which R^1 and R^2 are attached;

R^3 represents hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl(C_{1-6})alkyl, aryl, heteroaryl, arylcarbonyl, heteroarylcarbonyl or C_{1-6} alkylcarbonyl;

R⁴ represents arylsulphonyl, heteroarylsulphonyl, C₁₋₆ alkylsulphonyl, di(C₁₋₆)alkylaminosulphonyl, arylcarbonyl, C₁₋₆ alkylcarbonyl, heteroarylcarbonyl or C₁₋₆ alkoxy carbonyl; and

each R⁵ independently represents hydroxy, C₁₋₆ alkoxy, aryl(C₁₋₆)alkoxy, nitrile or halogen,
or a pharmaceutically acceptable salt or prodrug thereof.

14. A compound according to claim 13 in which R¹ and R² independently represent hydrogen, methyl, ethyl, propyl or benzyl, or R¹ and R² in combination represent pyrrolidinyl, piperidinyl, piperazinyl, 4-methylpiperazinyl or morpholinyl;

R³ represents hydrogen, methyl, ethyl, benzyl, allyl, propargyl, benzoyl, phenyl, thienyl or furoyl;

R⁴ represents benzenesulphonyl, naphthalene-2-sulphonyl, o-, m- or p-toluenesulphonyl, o-, m- or p-chlorobenzenesulphonyl, o-, m- or p-methoxybenzenesulphonyl, methanesulphonyl, dimethylaminosulphonyl, thienylsulphonyl, benzoyl, acetyl, furoyl or *tert*-butoxycarbonyl; and

R⁵ represents hydroxy, methoxy, ethoxy, propoxy, benzyloxy, nitrile, fluorine, chlorine or bromine.

15. A compound according to claim 13 in which p is zero; R¹ and R² are identical and represent hydrogen or methyl; R³ represents hydrogen or benzoyl; and R⁴ represents arylsulphonyl or dimethylaminosulphonyl.

16. A compound according to claim 15 selected from:

2-[1-(benzenesulphonyl)-1*H*-indol-4-yl]ethylamine;

N,N-dimethyl 2-[1-(benzenesulphonyl)-1*H*-indol-4-yl]ethylamine;

N,N-dimethyl 2-[1-(dimethylamino)sulphonyl-1*H*-indol-4-yl]ethylamine;

N,N-dimethyl 3-[1-(benzenesulphonyl)-1*H*-indol-4-yl]propylamine;

N,N-dimethyl 2-[1-(benzenesulphonyl)-2-benzoyl-1*H*-indol-4-yl]ethylamine;

and pharmaceutically acceptable salts and prodrugs thereof.

17. A compound according to claim 13 for use in therapy.

- 5 18. A pharmaceutical composition comprising a compound
 according to claim 13 in association with a pharmaceutically acceptable
 carrier.

ABSTRACT

INDOLE AND INDOLINE DERIVATIVES AS 5-HT₆ SELECTIVE LIGANDS

5

Three classes of indole and indoline derivatives are disclosed as ligands selective for the 5-HT₆ receptors, and hence of value in the treatment or prevention of CNS disorders, including Alzheimer's disease, Parkinson's disease, schizophrenia, depression and anxiety. A particular class, 1-substituted-4-(ω -*N,N*-dialkyl-aminoalkyl)indoles, are claimed as novel compounds.

10

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
DECLARATION AND POWER OF ATTORNEY



Assistant Commissioner for Patents
 Washington, D.C. 20231

As a below-named inventor, I hereby declare that I believe I am:

- ☐ the original, first and sole inventor; or
☒ an original, first and joint inventor along with the other inventors listed below, of the subject matter which is claimed and for which a patent is sought on the invention entitled

Indole and indoline derivatives as 5-HT6 selection ligands

the specification of which ☒ is attached hereto;

☐ was filed on _____

as Application

Serial No. _____

and was amended

through _____

(if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended as indicated above.

I acknowledge the duty to disclose to the Patent and Trademark Office all information known to me to be material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, §1.56.

Foreign Priority

I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate for the same invention having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)

Priority Claimed

Great Britain	9820113.0	15 September 1998	
Country	Number	Date Filed	Attorney Docket

☒ ☐

Yes No

Country	Number	Date Filed	Attorney Docket

☐ ☐

Yes No

Prior United States Filing

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below

Appln. Ser. No.	Filing Date	Attorney Docket
Appln. Ser. No.	Filing Date	Attorney Docket
Appln. Ser. No.	Filing Date	Attorney Docket
Appln. Ser. No.	Filing Date	Attorney Docket

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56 which occurred between the filing date(s) of the prior application(s) and the national or PCT international filing date of this application:

Appln. Ser. No.	Filing Date	Status	Attorney Docket
Appln. Ser. No.	Filing Date	Status	Attorney Docket
Appln. Ser. No.	Filing Date	Status	Attorney Docket
Appln. Ser. No.	Filing Date	Status	Attorney Docket
Appln. Ser. No.	Filing Date	Status	Attorney Docket
Appln. Ser. No.	Filing Date	Status	Attorney Docket

And I hereby appoint

J. L. McGinnis

D. L. Rose

Reg. No. 34,387

Reg. No. 26,332

Reg. No. _____

respectively and individually, as my attorneys or agents with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith. Please address all communications to:

Patent Department
Merck & Co., Inc.
P. O. Box 2000
Rahway, NJ 07065-0907

Telephone No. (732)594-

I hereby declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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Date	
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Citizenship	
Post Office Address (if different from above)	